ANNALS OF
INTERNAL MEDICINE

VOLUME 54 FEBRUARY, 1961 NUMBER 2

CLINICAL USE OF A NEW DIAGNOSTIC AGENT, METHOPYRAPONE (SU-4885), IN PITUITARY AND ADRENOCORTICAL DISORDERS * †

By E. M. GOLD, M.D.,‡ J. R. KENT, M.D.,§ and P. H. FORSHAM, M.D.,‖
San Francisco, California

DISORDERS involving the adrenocortical secretion of cortisol have become more precisely characterized within recent years as knowledge concerning pituitary-adrenal physiology has increased and as newer, more critical means of study have become available. The secretion of cortisol by the adrenal cortex is normally regulated by corticotropin discharged from the anterior pituitary gland in response to stimuli from the ventral hypothalamus.[1] A quantitative estimate of the adrenal component of this system became possible when various procedures employing corticotropin as a direct and specific stimulator of the adrenal cortices were developed.[2, 3] For qualitatively demonstrating the extent of adrenocortical regulation by corticotropin, the relative sensitivity of hypothalamic-hypophysial centers to suppression with potent glucocorticoids [4, 5] has proved useful, particularly in disorders involving excessive cortisol secretion. In assessing the capacity of the pituitary

* Received for publication July 16, 1960.
Presented in part at the Forty-first Annual Meeting of The American College of Physicians, San Francisco, California, April 4, 1960.
† Part of the study was carried out under Grants C-3995 and MY-3951 from the National Institutes of Health.
‡ Assistant Professor of Medicine, School of Medicine, University of Southern California, Los Angeles; formerly Assistant Research Physician, Metabolic Unit, University of California School of Medicine, San Francisco, California.
§ Trainee, National Institute for Arthritis and Metabolic Diseases, and Research Fellow, Metabolic Unit and Department of Medicine, University of California School of Medicine, San Francisco.
‖ Professor of Medicine and Pediatrics, Director of the Metabolic Unit for Research in Arthritis and Allied Diseases, University of California School of Medicine, San Francisco.
Requests for reprints should be addressed to P. H. Forsham, M.D., Metabolic Unit, University of California Medical Center, San Francisco 22, California.

to store and release corticotropin, some direct measurement of the circulating hormone would be ideal; however, the bioassay technics [6, 7] presently available remain principally research tools.

A clinically useful test for estimating pituitary corticotropin release was proposed recently by Liddle et al.,[8] a test based upon the oral administration of an amphenone-like inhibitor of cortisol synthesis, SU-4885 (generic name: methopyrapone). This agent, a di-pyridyl propanone, differs from amphenone in that it lacks serious toxicity and, in appropriate dosage, selectively inhibits only the 11-β-hydroxylase which converts 11-desoxycortisol to cortisol within the adrenal cortex. The subsequent fall in circulating cortisol leads to a compensatory discharge of corticotropin by the pituitary (Figure 1). Ganong and Gold have recently found that metho-

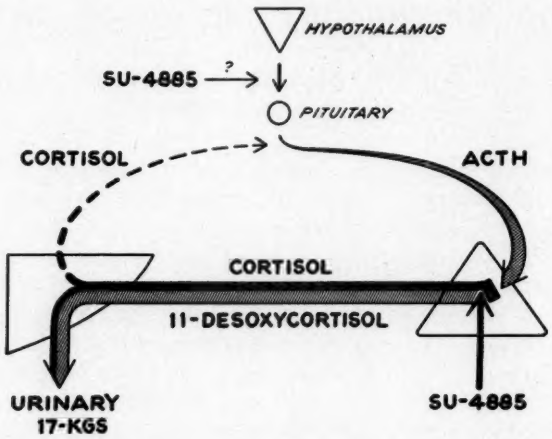


FIG. 1. Mechanism of corticotropin release induced by SU-4885 and estimation of response in urine as 17-ketogenic steroids (17-KGS).

pyrapone may have an additional action in directly stimulating the pituitary to release corticotropin in adrenalectomized dogs.[9] The importance of the latter mechanism in man remains to be elucidated. By either mechanism the adrenal cortex is stimulated by corticotropin to secrete large amounts of biologically inert 11-desoxycortisol, originally estimated by Liddle et al. as urinary Porter-Silber chromogens.[8] This result has been confirmed [10, 11] and better quantitated by administering SU-4885 intravenously and determining the subsequent 11-desoxycortisol increase as urinary 17-ketogenic steroids (17-KGS).[12]

The present report describes the use of SU-4885 as a test of corticotropin reserve and compares this procedure with others currently employed for evaluating pituitary and adrenal disorders.

Material and Methods

Eighty-six patients were given a standardized "intravenous SU-4885 test" in which 30 mg./Kg. of SU-4885 ditartrate * was infused for a 4-hour period. The material was dissolved in 1,000 ml. of 0.9% saline and infusions were usually begun between 8 and 10 A.M. Urine collections were started at the same time and continued for a period of 24 hours. Specimens were collected for similar periods on control days.

The additional studies carried out in selected patients consisted of: (1) an "adrenocortical stimulation test" in which 25 USP units of corticotropin † was given intravenously for eight hours and urine collected for a 24-hour period, beginning with the infusion, and (2) an "adrenocortical suppression test," in which a 24-hour urine specimen was obtained on the third day of administration of divided doses of dexamethasone ‡ (8 mg. daily) or 9-alpha-fluorohydrocortisone § (8 mg. daily).

The urine was analyzed for 17-KGS by a modification [3] of the Norymberski procedure,[13] and in certain selected cases Porter-Silber chromogens were measured by a modification [14] of the method of Reddy et al.[15]

Results

The normal subject given the intravenous SU-4885 test showed a significant increase in urinary 17-KGS within 12 hours, which returned toward base line by the end of 24 hours (Figure 2). The average 17-KGS rise

Table 1

RISE IN URINARY 17-KGS OUTPUT (Mg/24 hrs.) IN RESPONSE TO SU-4885

BASAL

SEX	NO.	RANGE	MEAN
MALE	8	7-25	15.4
FEMALE	10	9-15	12.7

SU-4885

		RISE OVER BASAL	
SEX	NO.	RANGE	MEAN
MALE	8	9-21	15.2
FEMALE	10	7-20	12.1

* SU-4885 ditartrate, of which 41.5% is the free base, was generously supplied by Dr. C. H. Sullivan, Ciba Pharmaceutical Products, Inc., Summit, N. J., who also supported the project with a grant-in-aid.

† Corticotropin Injection was kindly provided by Dr. H. C. Peltier of The Upjohn Company, Kalamazoo, Mich.

‡ Supplied as Decadron through the courtesy of Dr. E. Alpert, Merck, Sharp & Dohme, West Point, Pa.

§ Generously provided as Florinef by Dr. S. C. Sutton, E. R. Squibb & Sons, New York, N. Y.

during this 24-hour period amounted to from 12 to 15 mg. in 18 normal individuals (Table 1). Essentially no increase was found in panhypopituitarism or when SU-4885 was given together with 9-alpha-fluorohydrocortisone, a potent pituitary corticotropin suppressant (Figure 2). As shown in a patient previously subtotally adrenalectomized for Cushing's disease, only a partial response occurred when the amount of functioning adrenal tissue was markedly reduced (Figure 2).

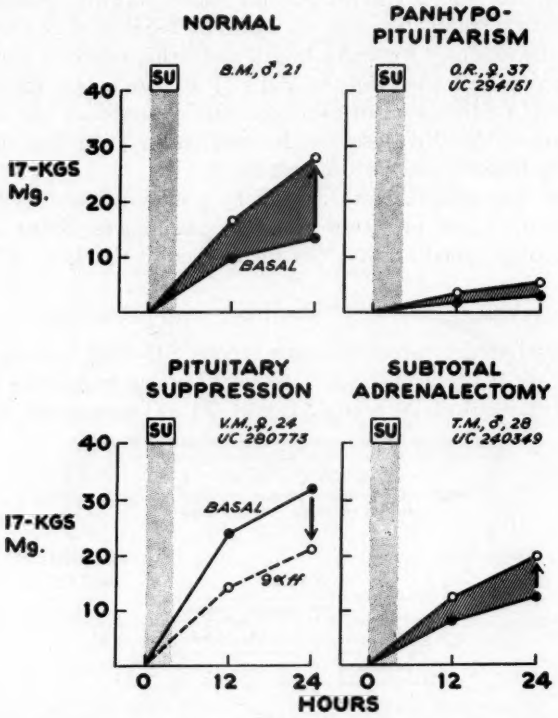


FIG. 2. Response to SU-4885 test in the normal subject, compared to response in patients with decreased pituitary corticotropin or decreased adrenal reserve.

Central nervous system lesions involving the hypothalamus inhibited response to SU-4885 in two of five patients with cerebral disorders (Figure 3). One of these, a 16-year-old boy manifesting obesity and narcolepsy after an apparent episode of encephalitis, responded not at all. The other, a 56-year-old woman with a roentgenographically demonstrated suprasellar aneurysm impinging upon the walls of the third ventricle, showed only a slight rise in 17-KGS after SU-4885. In both cases, the basal 17-KGS output was normal and rose significantly following infusions of ACTH.

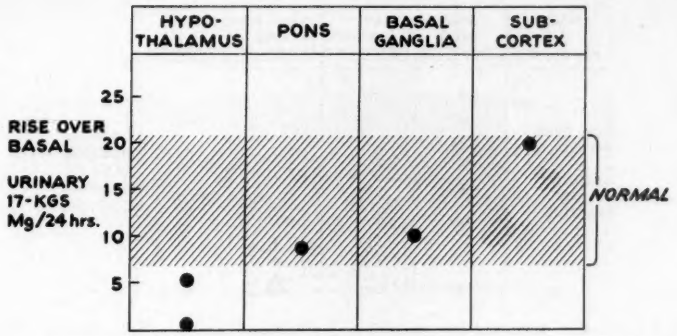


FIG. 3. Reduced SU-4885 response in patients with hypothalamic disorders compared to normal response in patients with central nervous system lesions in other sites.

Pituitary disorders may result in the failure of all tropic hormone secretions or selectively involve but one. Response to SU-4885 apparently was not impaired in the absence of growth hormone, gonadotropin, or antidiuretic hormone (Table 2). However, thyrotropin is indirectly required, inasmuch as hypothyroidism, either primary or pituitary in origin, limited responsiveness to SU-4885 (Table 2). It is of interest that hyperthyroidism also lowered the magnitude of response to SU-4885 in three cases studied (Table 2). Cachectic disorders may occasionally result in corticotropin failure, as indicated by the impaired SU-4885 response in one of three patients with anorexia nervosa (Table 2). Primary gonadal failure associated with high urinary gonadotropin titers did not impair response to SU-4885 (Table 2).

TABLE 2

Response to Intravenous SU-4885 Test in Various Endocrine Disorders

Patient	Diagnosis	Urinary 17-KGS (mg./24 hr.)	
		Basal	SU-4885 (I.V. Test)
L. R.	Primordial dwarfism	6.5	13.1
W. H.	Pituitary hypogonadism	10.7	17.7
S. H.	Diabetes insipidus	14.5	28.4
T. C.	Primary hypothyroidism	12.7	15.0
M. C.	Primary hypothyroidism	6.4	8.1
A. S.	Primary hypothyroidism	5.9	6.9
D. T.	Pituitary hypothyroidism	13.8	13.9
R. W.	Hyperthyroidism (Graves'dis.)	10.4	13.3
A. R.	Hyperthyroidism (Graves'dis.)	16.4	11.1
E. T.	Hyperthyroidism (Graves'dis.)	9.8	7.7
J. B.	Anorexia nervosa	10.9	9.4
G. P.	Anorexia nervosa	11.1	22.8
B. R.	Anorexia nervosa	10.6	21.1
E. J.	Ovarian failure (mumps)	10.2	23.8
D. W.	Klinefelter's syndrome	7.2	13.9

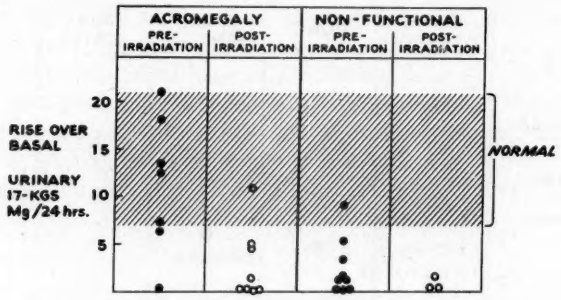


FIG. 4. SU-4885 response in patients with pituitary tumors. Note normal response in patients with acromegaly in contrast to patients with nonfunctional tumors, as well as the subnormal response following pituitary irradiation.

Expanding pituitary tumors causing enlargement of the sella turcica roentgenographically markedly reduce the rise in 17-KGS following SU-4885, with the exception of those secreting excessive amounts of growth hormone. Among seven of 16 patients with pituitary neoplasms who responded normally, six had manifest acromegaly (Figure 4). Following pituitary irradiation, consisting of an average of 4,000 r (pituitary dose) given over a period of three to five weeks, response to SU-4885 was diminished in almost every case of pituitary tumor (Figure 4). Therapy appeared to have effectively arrested growth hormone production as evidenced by the significant clinical improvement in those cases with acromegaly.

Surprisingly little deviation from normal *basal* 17-KGS output was noted in patients, with pituitary tumors, unresponsive to SU-4885. Urine specimens collected for 12-hour periods in nine such cases also disclosed that the excretion of 17-KGS throughout the day was normally distributed, being somewhat higher from 8 A.M. to 8 P.M. (5.9 mg.) than during the night

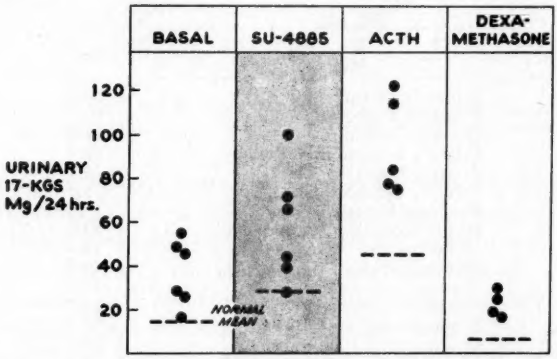


FIG. 5. Pituitary-adrenal function tests in bilateral adrenocortical hyperplasia.

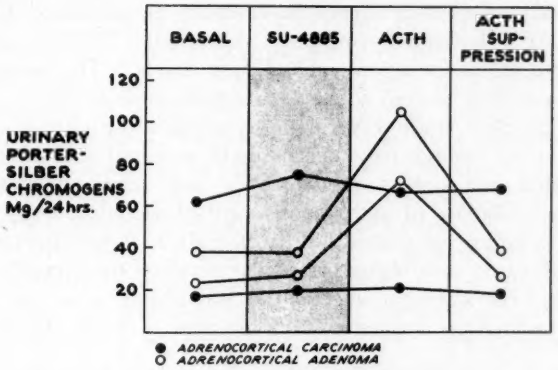


FIG. 6. Pituitary-adrenal function tests in unilateral adrenocortical tumors.

12 hours (4.5 mg.). In addition, in each of these cases a significant increase in urinary 17-KGS occurred following infusions of corticotropin.

Primary adrenocortical failure, while most convincingly demonstrated by the lack of response to administered corticotropin, is virtually excluded by a normal intravenous SU-4885 test since patients with decreased adrenocortical reserve show an impaired response to SU-4885 (Figure 2).

The diagnosis of adrenocortical hyperfunction often requires no more than the finding of high urinary levels of 17-KGS. However, the problem often remains as to whether the cortisol excess arises from a unilateral tumor or bilateral hyperplasia. This was studied with SU-4885 preoperatively in 10 cases where the pathologic lesion was later determined at operation. Six patients with bilateral hyperplasia, when given SU-4885, had a further increase in their already elevated 17-KGS output, demonstrating

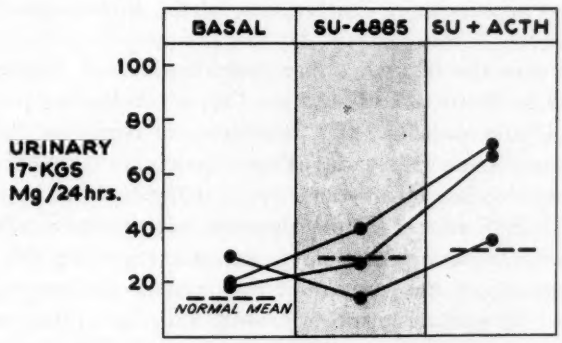


FIG. 7. Reduced response to SU-4885 in adrenocortical hyperplasia following subtotal hypophysectomy, pituitary irradiation, or both.

that additional endogenous corticotropin could be mobilized (Figure 5). Intravenous ACTH markedly increased the urinary 17-KGS and dexamethasone treatment caused a lowering of these levels. The findings in four patients subsequently proved to have tumorous adrenocortical overactivity differed significantly from those with hyperplasia (Figure 6). In these cases, little or no change from basal levels occurred following SU-4885, suggesting that endogenous corticotropin had been suppressed by the tumors. The existence of autonomous cortisol secretion was further supported by the failure of potent glucocorticoids to lower urinary 17-KGS output. Both cases with benign adenomas retained the capacity to respond to administered corticotropin whereas this was absent in the two carcinomas tested. These findings suggest that an elevated 17-KGS output which can

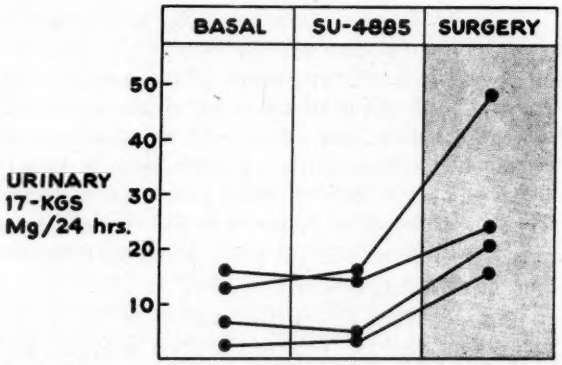


FIG. 8. Significant increase in urinary 17-KGS with surgical operation in patients with pituitary tumors and impaired SU-4885 response.

be further increased by SU-4885 strongly favors hyperplasia, whereas unresponsiveness appears more characteristic of the autonomous overactivity seen with tumors.

SU-4885 may also be useful when evaluating certain therapeutic measures occasionally beneficial in Cushing's disease. Following pituitary irradiation, in addition to definite clinical evidence of remission, three patients with hyperplasia manifested an impaired response to SU-4885 instead of the augmented response observed previously (Figure 7).

While SU-4885 affords useful diagnostic information concerning corticotropin reserve, a note of caution is necessary regarding the use of this agent to prognosticate the response of the pituitary-adrenal system to surgical trauma. Despite an impaired SU-4885 response in four patients with pituitary tumors, a significant rise in urinary 17-KGS occurred during craniotomy in each case (Figure 8).

Discussion

The present study indicates that disorders in cortisol production secondary to hypothalamic or pituitary abnormalities may be readily demonstrated by the intravenous SU-4885 test. The subnormal response noted in two patients with hypothalamic disorders emphasizes the corticotropin regulating role of the hypothalamus in man and, in addition, indicates that cerebral lesions involving this area may be localized functionally. In animals, experimental hypothalamic lesions regularly abolish rises in corticotropin secretion normally initiated by a variety of stressful stimuli,[16, 17] in contrast to frontal and temporal lobe ablation, which seems to augment corticotropin release.[18] Despite the defect in corticotropin release demonstrated in both hypothalamic disorders studied, it was noteworthy that the basal secretion of cortisol remained normal. This also resembles findings in animals with stereotaxic lesions of the hypothalamus [16] and suggests that corticotropin secretion may be regulated by two distinct mechanisms. One, hypothalamically mediated, appeared primarily responsive to nociceptive and other stimuli, such as SU-4885, which mobilize corticotropin to increase cortisol output above basal levels; the other, probably hypophysial, seems principally concerned with maintaining basal cortisol production from day to day. It would appear that the sensitivity of the former mechanism may be markedly reduced by relatively minor disturbances in hypothalamic or pituitary function. By contrast, as much as 70 to 90% of the pituitary must be destroyed before basal levels of cortisol fall off.[19, 20] While a loss of the normal diurnal variation in cortisol secretion has been noted in some cases of pituitary tumor,[21] no such impairment was evident in the present series of tumors found unresponsive to SU-4885. The association of an impaired response to SU-4885 together with normal basal urinary corticoid output has been noted by others [22] as well as ourselves in patients with anorexia nervosa, pituitary tumors, and following pituitary irradiation in cases of acromegaly and Cushing's disease. Such cases most likely have less extensive pituitary involvement than those in whom both basal 17-KGS excretion as well as response to SU-4885 are subnormal.

The impaired corticotropin secretion demonstrable with SU-4885 in patients with pituitary tumors provides an index of the functional progression of such neoplasms. In acromegaly, the eradication of a normal response by irradiation may prove useful for assessing the efficacy of therapy. The normal SU-4885 response in patients with untreated acromegaly, as opposed to the poor response observed with nonfunctional pituitary tumors, could arise from two separate and not mutually exclusive circumstances. The striking physical changes accompanying excessive growth hormone secretion may cause acidophile tumors to be detected earlier than are nonfunctioning intrasellar tumors. Secondly, growth hormone or an associated hypersecretion of corticotropin may maintain or even enhance adreno-

cortical sensitivity,[23, 24] thereby augmenting response to SU-4885 even when the reserve of pituitary corticotropin has been limited by a tumor.

While seemingly paradoxic, the subnormal response to intravenous SU-4885 noted in both hypo- and hyperthyroidism is consistent with several previous observations. In the absence of thyroid hormone, the metabolic decline in pituitary or adrenal activity, or both,[25, 26] as well as the slowed hepatic clearance of cortisol from the circulation,[27] may singly or in combination reduce the stores of pituitary corticotropin. An excessive secretion of thyroid hormone also could deplete pituitary corticotropin reserve since the more rapid removal of cortisol by the liver [27] might require a continued secretion of corticotropin in order to maintain normal circulating levels of cortisol, thereby leaving the pituitary with little or no corticotropin in reserve. These findings with the intravenous SU-4885 test in hyper-

	ADRENOCORTICAL SECRETORY FUNCTION		PITUITARY ACTH REGULATION	
	AT REST	ADRENAL RESERVE	ABSENT OR AUTONOMOUS	ACTH RESERVE
BASAL *CORTICOID OUTPUT*	+			
ACTH *STIMULATION TEST*		+		
ACTH *SUPPRESSION TEST*			+	
SU-4885 *TEST*		+	+	+

FIG. 9. Parameters of pituitary-adrenal function estimated by tests available for clinical use.

thyroidism differ from those of Liddle et al.,[22] who reported a normal responsiveness to oral SU-4885 in such cases. Preliminary testing in our laboratory by the standard intravenous procedure, but using 60 mg./Kg./4 hours of SU-4885, appears to have improved responsiveness in two hyperthyroid patients, suggesting that failure to respond may reflect rapid inactivation of SU-4885 in the hyperthyroid state.

Inasmuch as the degree of hypothalamic-pituitary impairment disclosed by the SU-4885 test may be slight, as well as limited to one specific type of stimulus, the interpretation of a subnormal response as an indication for replacement or supportive corticosteroid therapy requires further study. The isolated, and essentially complete, failure of the pituitary to secrete

corticotropin has been described in association with "Addisonian" crisis,[28] and episodes of transitory adrenal insufficiency have been noted in some patients, unresponsive to oral SU-4885, who nonetheless had normal basal levels of cortisol production.[22] However, in the present study, when four cases unresponsive to intravenous SU-4885 were subjected to operation, they not only showed a significant rise in urinary 17-KGS excretion, but in each instance the procedure was completed uneventfully and without the administration of supplementary hydrocortisone. This suggests that, as is found in the cortisone-treated rat, although pituitary ACTH content may be suppressed as much as 60%, a sufficiently intense stimulus, such as scalding, can deplete the pituitary of 50% of the remaining ACTH,[29] an amount apparently sufficient to increase cortisol output. The results thus far, however, would indicate that a normal SU-4885 response assures an adequate response of the pituitary-adrenal system to trauma.

SU-4885 is a useful diagnostic adjunct for screening aberrations in hypothalamic, pituitary, or adrenal function as well as for indirectly assessing pituitary corticotropin reserve (Figure 9). The use of the SU-4885 test in conjunction with corticotropin stimulation or corticoid suppression tests now makes it possible to localize pituitary-adrenal disorders more precisely by technics available for clinical use.

Summary

Eighty-six patients received standardized intravenous methopyrapone (SU-4885) in tests designed to evaluate ACTH reserve.

Compared to a normal rise in 24-hour urinary 17-ketogenic steroids of from 12 to 15 mg., patients with hypothalamic lesions showed a markedly reduced response, as did those with nonfunctioning pituitary tumors generally. However, when associated with acromegaly, the response was usually normal.

In the presence of Cushing's syndrome, a normal or greater than normal response was noted in patients with overactivity of the adrenal cortices in the absence of demonstrable tumors. In contrast, two cases of carcinoma and two cases of adenoma failed to show a significant rise in 17-ketogenic steroids, making this a useful differential point. Adrenal insufficiency and hypothyroidism, as well as uncontrolled hyperthyroidism, seemed to decrease the response to SU-4885 markedly.

Four cases with a poor preoperative response to SU-4885 showed a significant rise in urinary 17-ketogenic steroids in surgery, demonstrating that a negative response to SU-4885 does not necessarily call for corticoid coverage during operation.

Methopyrapone (SU-4885) appears to be a useful diagnostic adjunct in diseases of the hypothalamic pituitary adrenal area, provided that abnormalities of thyroid function and primary adrenal insufficiency have been ruled out.

ACKNOWLEDGMENT

We wish to acknowledge with gratitude the technical assistance of Anita Sarner, B.S., of San Francisco, California, in this work.

SUMMARIO IN INTERLINGUA

Octanta-sex patientes recipeva un standardisate test a methopyrapona (SU-4885) per via intravenose, le qual permitte un mesuration indirecte de augmentos del secretion de ACTH per le glandula pituitari anterior. SU-4885—in un dosage de 7,5 mg per kg per hora in le forma del bitartrato—esseva infundite in solution salin durante quatro horas, e le augmento del steroides 17-cetogenic (17-KGS) in un collection del urina de 24 horas esseva estimate. Esseva trovate que un augmento de 12 a 15 mg de 17-KGS urinari in 24 horas esseva un responsa normal. Esseva effectuate studios ancillari que includeva tests a ACTH intravenose, tests de suppression a dexamethasona, e le administration de SU-4885 conjunctemente con corticotrophina, con le objectivo de testar le responsivitate adreno-cortical per se in casos de un relative non-responsivitate a SU-4885. Varie lesiones del systema nervose central habeva nulle effecto super le resultatos del test a SU-4885, durante que un affection del hypothalamo reduceva le responsa marcatemente. Non-functionante tumores pituitari esseva associate con responsas subnormal in octo ex novem casos. In le none caso, le 17-KGS monstrava un augmento basso-normal. Per contrasto con isto, in le presentia de tumores pituitari que allargava le sella e que esseva associate con acromegalia, un responsa normal esseva trovate in quatro ex septe casos. In le altere tres casos, le responsa esseva basso-normal. Hyperplasia adrenocortical bilateral associate con syndrome de Cushing effectuava un responsa plus que normal in tres ex sex casos e un responsa normal in le altere tres, sed in duo subjectos con carcinoma adrenal e in duo con adenoma nulle augmento significative de 17-KGS esseva constatate. Iste constatation—per su contrasto con le responsa supranormal o normal in casos de hyperplasia adrenal bilateral—provide un simple e rapide test de diagnose differential.

Therapia a radios X e therapia chirurgic del glandula pituitari reduceva invariabilemente le responsa a SU-4885. In casos de insufficienta adrenal, le responsa a SU-4885 esseva marcatemente reducite o absente, de maniera que on pote concluder que un responsa normal exclude le possibilitate de hypoadrenocorticismo.

Tres ex tres casos de hypothyroidismo e un ex quatro casos de anorexia nervose con reducite nivellos del metabolismo basal revelava un responsa minime o absente in le standardisate test a SU-4885 intravenose. Hyperthyroidismo, testate in tres casos, esseva similemente accompaniate de non-responsivitate a SU-4885, lo que suggere le possibilitate de un acutemente diminuite reserva de ACTH in non-stabilisate hyperthyroidismo. On non debe expectar que le resultatos de iste relativemente celere test es semper de accordo con le resultatos obtenite per altere methodos que require duo o tres dies de administration oral de plus grande quantitates de droga.

In tres ex quatro casos de non-functionante tumores pituitari con minime o absente responsa a SU-4885, le intervention chirurgic esseva accompaniate de un augmento del 17-KGS. Isto pare indicar que un basse responsa a SU-4885 ante le operation non indica necessarimente que un therapia pre-operatori a reimplaciamento corticoidic es requirite sed plus tosto que le patiente debe esser tenite sub observation meticulose post le operation.

Il pare que methopyrapona (SU-4885) es un utile adjuncto diagnostic in le differentiation de varie aberrationes hypothalamo-pituitario-adrenal e etiam de certe typos de dysfunction thyroidic, gratias a su applicabilitate in le estimation indirecte del reservas de corticotropina pituitari.

BIBLIOGRAPHY

1. Harris, G. W.: Neural control of the pituitary gland. Arnold, London, 1955.
2. Renold, A. E., Jenkins, D., Forsham, P. H., Thorn, G. W.: The use of intravenous ACTH: a study in quantitative adrenocortical stimulation. J. Clin. Endocr. **12**: 763, 1952.
3. Gold, E. M., Starr, P.: Urinary excretion of 17-ketogenic steroids in normal subjects before and after stimulation with intramuscular zinc-ACTH. J. Clin Endocr. **19**: 907, 1959.
4. Jailer, J. W., Gold J. J., Wallace, E. Z.: Evaluation of "cortisone test" as diagnostic aid in differentiating adrenal hyperplasia from adrenal neoplasia. Amer. J. Med. **16**: 340, 1954.
5. Cope, C. L., Harrison, R. J.: Effect of 9-α-fluorohydrocortisone on adrenal hyperfunction in Cushing's syndrome. Brit. Med. J. **2**: 457, 1955.
6. Nelson, D. H., Hume, D. M.: Corticosteroid secretion in the adrenal venous blood of the hyphophysectomized dog as an assay for ACTH. Endocrinology **57**: 184, 1955.
7. Lipscomb, H. S., Nelson, D. H.: Measurement of corticosterone in rat adrenal venous plasma as a bioassay for ACTH. Fed. Proc. **18**: 95, 1959.
8. Liddle, G. W., Island, D., Lance, E. M., Harris, A. P.: Alterations of adrenal steroid patterns in man resulting from treatment with a clinical inhibitor of 11-β-hydroxylation. J. Clin. Endocr. **18**: 906, 1958.
9. Ganong, W. F., Gold, E. M.: The effect of SU-4885 on blood ACTH levels in adrenalectomized dogs. (In preparation.)
10. Jenkins, J. S., Meakin, J. W., Nelson, D. H., Thorn, G. W.: Inhibition of adrenal steroid 11-oxygenation in the dog. Science **128**: 478, 1958.
11. Gold, E. M., Bigler, R., Newman, S., Angers, M., DiRaimondo, V. C.: Studies of pituitary adrenocortical relationships with an 11-β-hydroxylase inhibitor of the adrenal cortex (abstract). Clin. Research **7**: 64, 1959.
12. Gold, E. M., DiRaimondo, V. C., Forsham, P. H.: Quantitation of pituitary corticotropin reserve in man by use of an adrenocortical 11-beta-hydroxylase inhibitor (SU-4885). Metabolism **9**: 3, 1960.
13. Norymberski, J. K.: Determination of urinary corticosteroids, Nature **170**: 1074, 1952.
14. Forsham, P. H., DiRaimondo, V., Island, D., Rinfret, A. P., Orr, R. H.: Dynamics of adrenal function in man, *in* The Human Adrenal Cortex, Vol. III, p. 279, Little, Brown and Company, Boston. 1955.
15. Reddy, W. J., Jenkins, D., Thorn, G. W.: Estimation of 17-hydroxycorticoids in urine. Metabolism **1**: 511, 1952.
16. Ganong, W. F., Hume, D. M.: Absence of stress-induced and "compensatory" adrenal hypertrophy in dogs with hypothalamic lesions. Endocrinology **55**: 474, 1954.
17. McCann, S. M.: Effect of hypothalamic lesions on the adrenal cortical response to stress in the rat. Amer. J. Physiol. **175**: 13, 1953.
18. Spell, J. P., Allen, M. B., Audy, O. J., Hardy, J. D.: Effect of selected brain lesions on plasma electrolyte and 17-21-hydroxycorticosteroid levels. Amer. J. Med. **27**: 325, 1959.
19. Van Buren, J. M., Bergenstal, D. M.: An evaluation of graded hypophysectomy in man. Cancer **13**: 155, 1960.
20. Ganong, W. F., Hume, D. M.: Effect of graded hypophysectomy on thyroid, gonadal, and adrenocortical function in dog. Endocrinology **59**: 293, 1956.
21. Hökfelt, B., Luft, R.: The effect of suprasellar tumours on the regulation of adrenocortical function. Acta endocr. **32**: 177, 1959.
22. Liddle, G. W., Estep, H. L., Kendall, J. W., Jr., Williams, W. C., Jr., Townes, A. W.: Clinical application of a new test of pituitary reserve. J. Clin. Endocr. **19**: 875, 1959.

23. Cushing, H., Davidoff, L. M.: The pathological findings in four autopsied cases of acromegaly with a discussion of their significance, Monograph 22, Rockefeller Institute for Medical Research, New York, 1927.
24. Daughaday, W. H., Perry, W. E., MacBryde, C. M.: Hyperadrenalcorticism in a case of acromegaly with insulin-resistant diabetes, J. Clin. Endocr. **10**: 410, 1950.
25. Levin, M. E., Daughaday, W. H.: The influence of the thyroid on adrenocortical function. J. Clin. Endocr. **15**: 1499, 1955.
26. Roy, S. N., Karkun, J. N., Sur, R. N.: Changes in the adrenal of hypothyroid (thiourea-induced) rats and the influence of testosterone propionate on such changes. Acta endocr. **27**: 216, 1958.
27. Peterson, R. E.: The influence of the thyroid on adrenal cortical function. J. Clin. Invest. **37**: 736, 1958.
28. Steinberg, A., Schechter, F. R., Segal, H. I.: True pituitary Addison's disease—a pituitary unitropic deficiency (15-year follow-up). J. Clin. Endocr. **14**: 1519, 1954.
29. Holub, D. A., Kitay, J. I., Jailer, J. W.: Effects of exogenous adrenocorticotropic hormone (ACTH) upon pituitary ACTH concentration after prolonged cortisone treatment and stress. J. Clin. Invest. **38**: 291, 1959.

ADDISON'S DISEASE ASSOCIATED WITH SOUTH AMERICAN BLASTOMYCOSIS * †

By Gildo Del Negro, M.D., M.P.H., Bernardo L. Wajchenberg, M.D., Virgilio G. Pereira, M.D., José Shnaider, M.D., A. B. de Ulhoa Cintra, D.M., Ph.D., L. Marques de Assis, M.D., and S. A. Prado Sampaio, M.D., *São Paulo, Brazil*

The systemic mycotic diseases as etiologic agents of chronic adrenal insufficiency have been considered in the medical literature. Thus, histoplasmosis,[1-5a] cryptococcosis,[2, 6] coccidioidomycosis,[7, 8] and North American blastomycosis [9-11] have been found to involve the adrenals. In some cases the clinical picture of Addison's disease has been produced.

South American blastomycosis is a systemic fungus disease, the visceral lesions of which frequently appear in the adrenals at autopsy. Extensive destruction of the adrenal glands has been reported, but no studies of adrenal function based on adrenocortical stimulation tests had been done ante-mortem. It is the purpose of this paper to report three cases of Addison's disease occurring in patients with South American blastomycosis.

Methods

Confirmation of the clinical impression was sought by standard methods. The water loading test of Robinson, Power, and Kepler [12] was used for screening purposes in cases 1 and 2, and the test of Soffer and Gabrilove [13] in case 3. In case 2 the test was not conclusive because of the very high nocturnal volume of urine. Chloride determinations on blood and urine samples were made by the Schales and Schales method.[14] Blood and urine urea levels were measured by the method of Gentzkow.[15]

Serum sodium and potassium were measured using a flame photometer. Blood sugar was determined by the Nelson modification [16] of the Somogyi method.

Measurements of total urinary 17-hydroxycorticosteroids were made according to the method of Butt et al.[17] The 17-ketosteroids were measured by the method of Drekter et al.[18]

The steroid stimulation test was performed as suggested by Jenkins et al.[19] Twenty-five milligrams of adrenocorticotropic hormone (ACTH) in 500 ml. of 5% dextrose solution were given intravenously during a period of eight hours on two successive days. Determinations of 17-ketosteroids and 17-hydroxycorticosteroids were carried out on 24-hour urine collections during two control days and during the two days of ACTH stimulation.

The complement fixation test for the diagnosis of the serologic status of patients with South American blastomycosis was performed according to the Fava Netto adaptation [20] of the Wadsworth, Maltaner, and Maltaner method for quantitative complement fixation determinations. Titers between zero and 2.0 were considered negative. According to Fava Netto's experience, based upon more than 300 cases, the titers increase when the disease disseminates and decrease as the patient improves.

* Received for publication July 26, 1960.

† From the Department of Tropical Medicine and Infectious diseases and the First Medical Clinics, Hospital das Clinicas, University of São Paulo Medical School, São Paulo, Brazil.

Requests for reprints should be addressed to Gildo Del Negro, M.D., Hospital das Clinicas, Fac. de Med. da Universidade de São Paulo, Caixa Postal 8091, São Paulo, Brazil.

Case Reports

Three adult males with definite clinical and laboratory evidence of South American blastomycosis were the subjects of this study. The clinical course of each suggested the development of Addison's disease.

Case 1. A 46-year-old white male developed ulceration of the soft palate and uvula in 1952. Mild cough and dysphagia were present. Biopsy of one of the ulcers revealed *Paracoccidioides* (*Blastomyces*) *brasiliensis*. Treatment with sulfadiazine produced healing of the ulcers for several months after treatment was discontinued by the patient. Recurrence was accompanied by extension to the larynx. Subsequent treatment was irregular until late 1957 when he became more cooperative because of increasing symptoms.

During 1958 there was gradual progression of anorexia, weight loss, and weakness despite daily administration of sulfadiazine. He was admitted to the Hospital das Clinicas on September 12, 1958 with a two-week history of dyspnea, dizziness, low-grade fever, vomiting, and inability to maintain the erect position.

Physical examination revealed an undernourished and dehydrated white male. Temperature was normal, the pulse 100, blood pressure 80 mm. Hg systolic and 50 mm. Hg diastolic while recumbent, 50 mm. Hg systolic and zero diastolic when erect.

TABLE 1

Addison's Disease Associated with South American Blastomycosis
Summary of Clinical Data

Case No.	Age	Sex	Asthenia	Weight Loss	Gastrointestinal Disturbances	Neuropsychiatric Symptoms	General Status	Blood Pressure (mm.Hg)		Abnormal Pigmentation	Clinical Manifestations of Blastomycosis
								Recumbent	Erect		
1	46	M	Severe	Yes	Anorexia Vomiting	Nervousness Insomnia	Poor	80/50	50/0	No	Stomatitis Bilateral lung involvement
2	47	M	Severe	Yes	Anorexia Abdominal pain	Dizziness Insomnia Apathy	Fair	60/40	?	Yes	Tongue ulcer Lung involvement
3	48	M	Severe	Yes	Anorexia Vomiting Diarrhea	Dizziness Headache Apathy	Poor	80/55	58/45	No	Lung and CNS(?) involvement

The peripheral lymph nodes were palpable but neither splenomegaly nor hepatomegaly was noted. A small area of active blastomycotic stomatitis was present. The essential clinical data are shown in Table 1.

The admission hemogram showed an erythrocyte concentration of 4,600,000, a hemoglobin of 14.1 gm.%, and a white blood cell count of 11,200, of which 43% were neutrophils, 22% were eosinophils, 28% were lymphocytes, and 7% were monocytes. Urinalysis was normal. *Mycobacterium tuberculosis* could not be found in the sputum, or in the gastric and bronchial washings. Quantitative complement fixation test showed a titer of 9.7 units.

The chest roentgenogram showed bilateral peribronchiolar infiltration with multiple small nodules, slight decrease in cardiac size, and anatomic emphysema (Figure 1).

Adrenal cortical insufficiency was suspected and this suspicion was strengthened by the water loading test and a single urinary 17-hydroxycorticosteroid determination. The results of the Robinson, Power, and Kepler test and the admission blood chemistries are shown in Table 2.

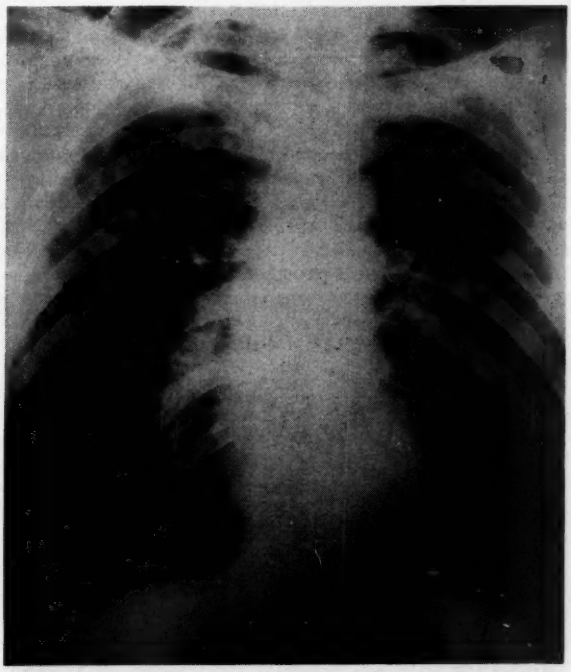


FIG. 1. Appearance of the chest of case 1 by x-ray examination during the first admission, October, 1958. Note microcardia and the diffuse infiltration in both lung fields.

TABLE 2

Addison's Disease Associated with South American Blastomycosis
Laboratory Findings on Admission

Case No.	Water Loading Test	Fasting Blood Sugar, mg./100 ml.	Blood Urea Nitrogen, mg./100 ml.	CO_2 mM./L.	Chlorides, mEq./L.	Sodium, mEq./L.	Potassium, mEq./L.	Titer of C.F. Test for Blastomycosis
1*	NV = 205 ml. DV = 30 ml. A = 1.5	81.0	60.0	20.4	84.0	129.0	6.1	9.7
2*	NV = 1.300 ml. DV = 380 ml. A = 15.8	68.0	36.0	18.7	84.0	130.0	5.9	4.7
3†	Ingested vol.: 1,500 ml. Five hours' diuresis: 200 ml.	74.0	19.0	23.8	—	131.0	5.2	15.0

* Robinson, Power, and Kepler test. NV = night urine volume. DV = maximum hourly daytime urine volume.

$$A = \frac{\text{Urine urea (mg./100 ml.)}}{\text{Plasma urea (mg./100 ml.)}} \times \frac{\text{Plasma chloride (mg./100 ml.)}}{\text{Urine chloride (mg./100 ml.)}} \times \frac{DV}{NV}.$$

† Soffer and Gabrilove test.

The response to oral prednisone, desoxycorticosterone acetate, and parenteral fluids was adequate. He was discharged on October 27, 1958 with instructions to take 10 mg. of prednisone daily, intramuscular desoxycorticosterone acetate, and 0.5 gm. per day of sulfamethoxypyridazine to control his blastomycosis.

The patient failed to maintain treatment, and weakness, anorexia, nervousness and an eight pound weight loss occurred progressively until readmission became necessary on January 13, 1959. No active blastomycotic lesions were found. Hypotension was present as before. Mild icterus was observed. Laboratory studies were entirely consistent with the clinical impression of infectious hepatitis. It was necessary to keep him in the hospital until April 27, 1959 in order to achieve satisfactory convalescence from his hepatitis and regulate his hypoadrenocorticalism.

Despite his past experiences, the patient discontinued medications within a week of discharge. When he contracted a respiratory infection, profound weakness, dehydration, and hypotension reappeared rapidly. At the time of hospitalization on May 20, 1959, he was unable to stand. The adrenocortical stimulation tests were carried out during this hospitalization (Table 3).

TABLE 3

Addison's Disease Associated with South American Blastomycosis
ACTH Tests

Case No.	Control		1st Day		2nd Day	
	17-OH* mg./day	17-KS† mg./day	17-OH mg./day	17-KS mg./day	17-OH mg./day	17-KS mg./day
1	3.2 3.6	—	2.6	—	1.6	—
2	5.3	5.8	5.0	3.8	8.9	2.8
3	7.1 9.3	2.9 3.2	14.3	4.4	4.0	4.5

* Normal: 11.8, S.D. ± 1.67 mg./24 hrs.
† Normal: 9–20 mg./24 hrs.

The response to treatment was adequate. Because the complement fixation test for South American blastomycosis had become negative and the erythrocyte sedimentation rate normal, treatment with the sulfonamide was discontinued. He has been maintained on oral prednisone and intramuscular desoxycorticosterone acetate through the outpatient clinic. Considerable clearing of the pulmonary infiltration, especially in the left lung, and increase in the cardiac size can be seen in Figure 2.

Case 2. In 1954, this male patient developed periodontal ulceration with loosening of the maxillary teeth. Extraction of the teeth and alveolar biopsy established a diagnosis of South American blastomycosis. The patient took sulfadiazine for two years with evident healing of the ulcers. The drug was discontinued and relapse occurred one year later; lesions were present in the lips, tongue, chin, and chest. These ulcers healed after sulfadiazine therapy was resumed.

In September, 1958, he began to complain of anorexia, apathy, insomnia, and abdominal pain. He noted dizziness upon rising from the recumbent or sitting position. His skin darkened and black freckles appeared on his hands. Weakness was progressive and accompanied by a weight loss of 36 pounds.

He was admitted to the Hospital das Clinicas on April 3, 1959. Physical examination revealed a 47-year-old white male with obvious pigmentary changes of the skin and lips. The heart sounds were faint. The blood pressure was 60 mm. Hg

systolic and 40 mm. Hg diastolic while recumbent; it was unobtainable in the erect posture. He was afebrile. The liver was palpable 1 cm. below the right costal margin. Although no active blastomycotic lesions were found during the admission examination, a small lingual ulcer appeared several weeks later. *Paracoccidioides (Blastomyces) brasiliensis* was demonstrated on biopsy of this lesion. The significant clinical findings are shown in Table 1.

The admission hemogram showed a hemoglobin concentration of 12.3 gm.% and a white blood cell count of 12,300, of which 62% were neutrophils, 25% lymphocytes, 8% eosinophils, and 5% monocytes. Urinalysis was normal. The blood chemistries are recorded in Table 2. The adrenocortical stimulation test was done and the results are shown in Table 3.

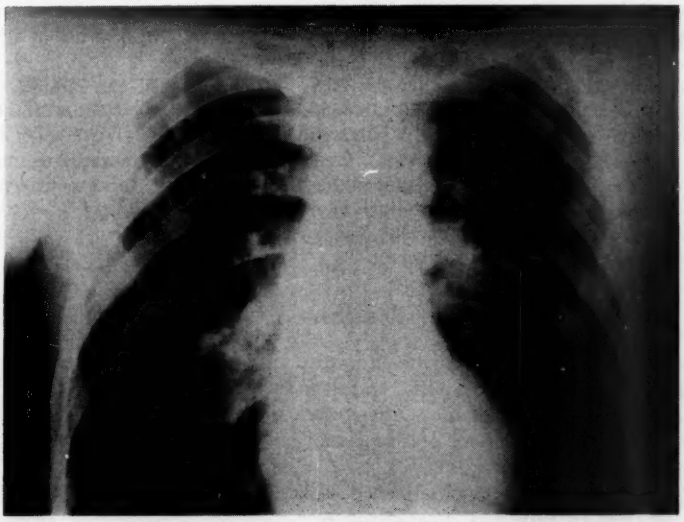


FIG. 2. Appearance of the chest of case 1 by x-ray examination in January, 1959. Note increase in cardiac size and clearing of the pulmonary infiltration which occurred during treatment with sulfonamides and substitution corticoid therapy.

A chest roentgenogram revealed small nodules bilaterally and minor fibrotic infiltration in the left upper lobe. There was nothing to suggest active pulmonary disease.

Since both the laboratory and clinical evidence justified a diagnosis of Addison's disease, treatment with oral prednisone and intramuscular desoxycorticosterone acetate was started and has been maintained to date. Sulfadiazine was given for the recurrent South American blastomycosis. He is being followed in the outpatient clinic.

Case 3. This Japanese male was unable to give an accurate past history. He had developed destructive lesions of the uvula and palate some years ago, which healed after prolonged sulfadiazine therapy. However, he continued to have some nasal regurgitation of food.

In November, 1958, he first noted malaise, dizziness, impaired vision, headache, and loss of weight. Weakness was progressive until February, 1959, when walking became difficult. A productive cough appeared in April, 1959.

He was admitted to the Hospital das Clinicas on May 7, 1959 because of severe weakness and dehydration. Physical examination revealed a 48-year-old male without pigmentary changes. The blood pressure was 80 mm. Hg systolic and 55 mm. Hg diastolic while recument, and 58 mm. Hg systolic and 45 mm. Hg diastolic while standing. The uvula and soft palate were partially destroyed and the left vocal cord was paralyzed. The tonsils were inflammed and enlarged. The significant clinical features appear in Table 1.

The admission hemogram showed: RBC 3,100,000, hemoglobin, 10.4 gm., WBC 12,000, of which 87% were neutrophils, 8% lymphocytes, 1% eosinophils, and 4% monocytes. Urinalysis was normal. The erythrocyte sedimentation rate was 58 mm. in one hour. The cerebrospinal fluid was normal. *Paracoccidioides* (*Blastomyces*) *brasiliensis* was present in the sputum. *M. tuberculosis* could not be found in the sputum. Skull roentgenograms and the electroencephalogram were normal. The chest roentgenogram showed small nodules bilaterally with dense fibrotic infiltrates.

Since the South American blastomycosis was active and the clinical picture suggested adrenal cortical insufficiency, blood chemistry determinations were immediately followed by the adrenocortical stimulation test (Tables 2, 3).

A diagnosis of adrenal cortical insufficiency was made and appropriate treatment given. He became ambulatory, regained his appetite, and was normotensive. He was discharged on September 12, 1959 to continue taking oral prednisone, intramuscular desoxycorticosterone acetate, and sulfamethoxpyridazine. He remains in fair health under outpatient supervision.

Discussion

We found several cases in the literature of adrenal involvement in reports of post-mortem studies of South American blastomycosis. Lima,[21] reviewing the first 33 autopsied cases of South American blastomycosis in the Pathology Department of the University of São Paulo School of Medicine, observed seven with adrenal involvement (21.2%). No clinical data were mentioned. Previously, several authors had published isolated reports of adrenal localization in systemic South American blastomycosis.[22-28]

Torres et al.[29] made the first detailed pathologic description of the adrenal lesions in South American blastomycosis. Caseation necrosis was prominent and apparently a consequence of local ischemia due to embolism by large fungus-containing cells. Embolism was associated with vasculitis and granuloma formation. Silva et al.[30] in a case of caseation paracoccidioidal necrosis of the adrenals, made a retrospective diagnosis of Addison's disease. This same case was later published by Motta [31] with a detailed pathologic description.

One of us (G. D. N.) studied two cases of South American blastomycosis with probable Addison's disease.[32, 33] The first case, a 31-year-old white male with central nervous system blastomycosis, presented asthenia, hyperpigmentation, positive water loading test (A values = 2,3), no eosinophil response to subcutaneous ACTH, and a flat oral glucose tolerance test with reactive hypoglycemia. Follow-up study was not possible in this patient. The second case was a 52-year-old white male with progressive asthenia, anorexia, and weight loss who died in Addisonian crisis before endocrine studies could be done. Necropsy showed isolated caseation paracoccidioidal necrosis of the adrenals. This case was also reported by Motta.[31]

Assis et al.[34] in a study of eight cases of Addison's disease observed clinically at the University of São Paulo Medical School reported two in which South American blastomycosis was found. A possible etiologic relationship was suggested.

The three cases reported here all had clinical and laboratory evidence of disseminated South American blastomycosis of considerable duration. As previously stated, adrenal involvement was observed in more than 20% of one series of autopsied cases of South American blastomycosis,[21] and isolated adrenal involvement was noted in two.[31] It is probable that many patients with dissemination of this fungus disease exhibit varying degrees of decreased adrenocortical function. Nevertheless, we have been unable to find any clinical studies of patients with South American blastomycosis in which adrenocortical stimulation tests, followed by steroid assays, were done.

The diagnosis of Addison's disease was suspected in each of these three patients on purely clinical grounds. Stimulation of the adrenal cortex by intravenous adrenocorticotropic hormone on two successive days failed to produce a normal response in 17-ketosteroid production in cases 2 and 3. There was likewise no increase in urinary 17-hydroxycorticosteroids in case 1. There was an increase in urinary 17-hydroxycorticosteroids on the second day in case 2 and on the first day in case 3. However, these increases were considerably less than those expected from a normal gland (100 to 300% increase in the first day, and 300 to 500% in the second).[35] All control levels were significantly below the normal levels for our laboratory.[35]

We believe a diagnosis of Addison's disease is justified in all three cases based on both the clinical and the laboratory evidence. Proof of the relationship of South American blastomycosis to the adrenal hypofunction cannot be obtained until necropsy. Nevertheless, the absence of other recognized etiology and the known frequency of adrenal involvement by South American blastomycosis make the assumed relationship probable.

All three patients have responded satisfactorily to substitution therapy for their adrenal insufficiency. The activity of their blastomycosis has apparently regressed during sulfonamide therapy, but they must be watched carefully because of the frequency of relapse.

Summary

1. Three cases of Addison's disease associated with proved South American blastomycosis are reported. All patients are alive and in fair health under substitution therapy.

2. Electrolyte and hormonal studies substantiated the clinical impression of Addison's disease.

3. South American blastomycosis should be considered as another entity which may produce the clinical picture called "Addison's disease."

Acknowledgments

Acknowledgments are due to Dr. John H. Seabury, Professor of Medicine at the Louisiana State University School of Medicine, New Orleans, La., for assistance in the preparation of the manuscript; to Dr. João Alves Meira, Professor of Infectious Diseases and Tropical Medicine at the University of São Paulo Medical School; and to Dr. Celeste Fava Netto for having performed the complement fixation tests in our patients.

SUMMARIO IN INTERLINGUA

Le autores describe tres casos de morbo de Addison associate con documentate blastomycosis sud-american.

Le tableau pathologic (i.e. le tableau de necrosis caseational) del localisation adrenal de iste mycosis systemic e certe datos clinic, incluse datos relative al 17-cetosteroides urinari, se trova reportate in le litteratura. Tamen, tests de stimulation adrenocortical (per medio de ACTH intravenose) con mesuration del nivellos urinari de 17-hydroxycorticosteroide ha non previemente essite executate in iste condition.

In le casos hic reportate, le diagnose de morbo de Addison esseva suspicite super le base de indicios clinic (asthenia, perdita de peso, perturbation gastro-intestinal e nervose, pigmentation, basse tension de sanguine, etc.). Omne le tres patientes monstrava un responsa anormal a cargation aquose; omnes habeva basse nivellos seral de natrium. Hyperkaliemia esseva observate in duo del casos.

Le nivellos de controlo pro 17-cetosteroide e 17-hydroxycorticosteroide urinari esseva infra le norma. Le responsivitate adrenal esseva absente o significativemente infra le nivello a expectar in le presentia de un glandula normal.

Es concludite que blastomycosis sud-american deberea esser considerate como un possibile etiologia additional de chronic insufficientia adrenal in areas endemic.

BIBLIOGRAPHY

1. Parsons, R. J., Zarafonetis, C. J. C.: Histoplasmosis in man. Arch. Intern. Med. **75**: 1, 1945.
2. Rawson, A. J., Collins, L. H., Grant, J. L.: Histoplasmosis and torulosis as causes of adrenal insufficiency. Amer. J. Med. Sci. **215**: 363, 1948.
3. Pinkerton, H., Iverson, L.: Histoplasmosis: three fatal cases with disseminated sarcoid-like lesions. Arch. Intern. Med. **90**: 456, 1952.
4. Vivian, D. N., Week, L. A., McDonald, J. R., Claggett, O. T., Hodgson, C. H.: Histoplasmosis: clinical and pathological study of 20 cases. Surg., Gynec., Obstet. **99**: 53, 1954.
5. Crispell, K. R., Parson, W., Hamlin, J., Hollifield, G.: Addison's disease associated with histoplasmosis. Amer. J. Med. **20**: 23, 1956.

5a. Rubin, H., Furcolow, M. L., Yates, J. L., Brasher, C. A.: The course and prognosis of histoplasmosis. Amer. J. Med. **27**: 278, 1959.

6. Rigdon, R. H., Kirksey, O. T.: Mycotic aneurysm (cryptococcosis) of the abdominal aorta. Amer. J. Surg. **84**: 486, 1952.
7. Forbus, W. D., Besterbreurtje, A. M.: Coccidioidomycosis: a study of 95 cases of the disseminated type with special reference to the pathogenesis of the disease. Milit. Surg. **99**: 653, 1946.
8. Maloney, P. J.: Addison's disease due to chronic disseminated coccidioidomycosis. Arch. Intern. Med. **90**: 869, 1952.
9. Martin, D. J., Smith, D. T.: Blastomycosis: a review. Amer. Rev. Tuberc. **39**: 275, 1939.
10. Kunkel, W. M., Week, L. A., McDonald, J. R., Claggett, O. T.: North American blastomycosis—Gilchrist's disease: a clinicopathological study of ninety cases. Surg., Gynec., Obstet. **99**: 1, 1954.
11. Fish, R. G., Takaro, T., Lovell, M.: Coexistent Addison's disease and North American blastomycosis. Amer. J. Med. **28**: 152, 1960.
12. Robinson, F. J., Power, M. H., Kepler, E. J.: Two new procedures to assist in the recognition and exclusion of Addison's disease; a preliminary report. Proc. Mayo Clin. **16**: 577, 1941.
13. Soffer, L. J., Gabrilove, J. L.: Simplified water loading test for the diagnosis of Addison's disease. Metabolism **1**: 504, 1952.

14. Schales, O., Schales, S. S.: Simple and accurate method for the determination of chloride in biological fluids. J. Biol. Chem. **140**: 879, 1941.
15. Gentzkow, C. J.: An accurate method for the determination of blood urea nitrogen by direct nesslerization. J. Biol. Chem. **143**: 531, 1942.
16. Nelson, N.: A photometric adaptation of the Somogyi method for the determination of glucose. J. Biol. Chem. **153**: 375, 1944.
17. Butt, W. R., Kornel, L., Morris, R.: The determination of 17-OH-corticosteroids in urine. Acta endocrinol. **26**: 65, 1957.
18. Drekter, I. J., Heisler, A., Scism, G. R., Stern, S., Pearson, S., McGavack, T. H.: The determination of urinary steroids. I. The preparation of pigment-free extracts and a simplified procedure for the estimation of total 17-ketosteroids. J. Clin. Endocr. **12**: 55, 1952.
19. Jenkins, D., Forsham, P. H., Laidlaw, J. C., Reddy, W. J., Thorn, G. W.: Use of ACTH in diagnosis of adrenal cortical insufficiency. Amer. J. Med. **18**: 3, 1955.
20. Fava Netto, C.: Estudos quantitativos sôbre a fixação de complemento na Blastomicose Sul-Americana, com antígeno polissacarídico. Thesis, Arq. Cir. Clin. Exper. **18**: 197, 1955.
21. Lima, F. X. P.: Contribuição ao estudo clinico e terapeutico da Blastomicose Sul-Americana visceral. Thesis, Univ. of S. Paulo School of Medicine, Brazil, 1952.
22. Vianna, G. O.: Doença de Posadas-Wernicke nas lesões apendiculares. Arq. Bras. Med. **4**: 446, 1914.
23. Mazza, S., Palamedi, B.: Caso mortal de blastomicosis cutaneo-mucosa. 7th meeting Soc. Arg. Pat. Reg. del Norte **7**: 424, 1932.
24. Azevedo, A. P.: Blastomicose da glandula suprarrenal por *C. immitis*, sem lesões linfaticas e com focos de fibrose nos pulmões. Mem. Inst. Osvaldo Cruz **29**: 189, 1934.
25. Boggino, J., Insaurralde, C., Prieto, R.: Tercer caso nacional de granuloma paracoccidioidico. An. Fac. Cienc. Med. Assunción (Paraguay) **11**: 21, 1938.
26. Prado, A. A.: Blastomicose dos pulmões e das cápsulas suprarrenais. Sindrome de cardiaco negro. An. Fac. Med. Univ. S. Paulo **20**: 215, 1944.
27. Chiriffe, A.: La paracoccidioidosis en el Paraguay. An. Fac. Cienc. Med. Assunción **4**: 9, 1944.
28. Fialho, A. S.: Localizações pulmonares da micose de Lutz. Anatomia Patologica e patogenia. Thesis, Rio de Janeiro, 1946.
29. Torres, M., Duarte, E., Guimarães, J. P., Moreira, L. F.: Destructive lesion of the adrenal gland in South American Blastomycosis (Lutz's disease). Amer. J. Path., **28**: 145, 1952.
30. Silva, U. A., Montenegro, M. R., Inague, T.: Doença de Addison de origem blastomicotica. Rev. Paul. Med. **41**: 258, 1952.
31. Motta, L. C.: Granulomatose paracoccidioidica: Forma organica isolada. Rev. Hosp. Clin. **11**: 353, 1956.
32. Negro, G. Del, Albuquerque, F. J., Campos, E. P.: Localização nervosa da Blastomicose Sul-Americana. Revisão da literatura e registro de dois casos. Rev. Hosp. Clin. **9**: 64, 1954.
33. Castro, R. M., Negro, G. Del, Bassoi, O. N., Faria, C. V.: Dificuldades diagnosticas na Blastomicose Sul-Americana. A proposito de oito casos. Rev. Paul. Med. **53**: 479, 1958.
34. Assis, L. M., Bloise, W., Coelho Netto, A. S., Burattini, E. L., Guerios, M. F. M., Epps, D. R., Borelli, A., Flosi, A. Z., Cintra, A. B. U.: Oito casos de doença de Addison. A Blastomicose Sul-Americana como possivel fator etiologico em dois. Rev. A. M. B. **5**: 56, 1959.
35. Wajchenberg, B. L., et al.: Studies on the adrenal responsiveness to intravenous ACTH. To be published.

THE SUCCESSFUL MANAGEMENT OF HEPATOLENTICULAR DEGENERATION WITH PENICILLAMINE: STUDIES ON THREE GENERATIONS OF A FAMILY *†

By JACK B. STRONG, JR.,‡ HUGH DEMPSEY, M.D., and S. RICHARDSON HILL, JR., M.D., *Birmingham, Alabama*

INTRODUCTION

HEPATOLENTICULAR degeneration (HLD, Wilson's disease)[1] is associated with abnormal deposition of copper in the brain, liver, kidneys, and other body tissues,[2] apparently due to an inherited defect in copper metabolism.[3] Clinically the disorder is manifested by signs and symptoms of basal ganglia disease, postnecrotic hepatic cirrhosis,[4] Kayser-Fleischer rings,[5] hypoceruloplasminemia, hypocupremia, hypouricemia, cupruresis, and aminoaciduria.[6] In light of our present state of knowledge concerning the pathogenesis of this disease, rational therapy should aim at producing a negative copper balance. This may be done both by decreasing copper intake and absorption, and by removing the excess copper deposition in tissue before irreversible damage occurs.[7] Chelating agents such as British anti-lewisite

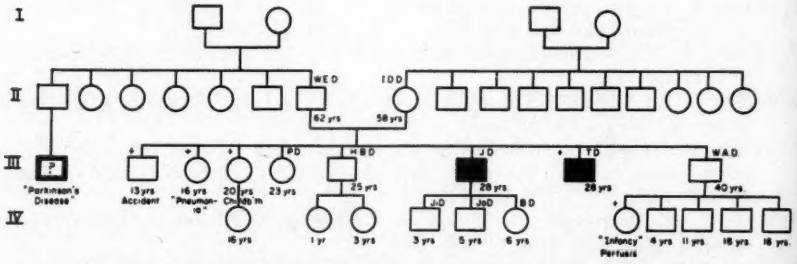


FIG. 1. Pedigree of propositus J. D. Initials in the right upper corner indicate kindred studied (Table 1); numerals in right lower corner indicate age at time of study or at time of death (+). Historical evidence of HLD could not be elicited in the grandparents, the parents, maternal uncles, or aunts. Except for a cousin, no history suggestive of HLD was discovered in the paternal branch of this family.

* Received for publication June 25, 1960.

From the Division of Metabolism and Endocrinology, the Department of Medicine and the University Hospital, University of Alabama Medical Center, and the Medical Service, Veterans Administration Hospital, Birmingham, Alabama.

† This study was aided in part by Grants 2A-5053, A-1265, and A-3555 from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, Bethesda, Md., and by funds from the Upjohn Company, Kalamazoo, Mich.

‡ Student Research Fellow in Metabolism, National Institutes of Health.

Requests for reprints should be addressed to S. Richardson Hill, Jr., M.D., Associate Professor of Medicine, The University of Alabama Medical Center, Medical College of Alabama, Birmingham 3, Alabama.

TABLE 1

Serum Ceruloplasmin and Total Serum Copper Levels in Three Generations of the Patient's Family

Subject	Relationship to Patient	Serum Ceruloplasmin (mg./100 ml.)	Total Serum Copper (μg./100 ml.)
J. D.	Patient	0	45
W. E. D.	Father	25.0	—
I. D. D.	Mother	33.0	—
W. A. D.	Brother	28.0	116
H. B. D.	Brother	26.0	104
P. D.	Sister	—	110
B. D.	Daughter	36.0	—
Jo. D.	Son	45.0	—
Ji. D.	Son	41.0	—

(BAL—2,3-dimercaptopropanol) and calcium versenate (calcium disodium ethylenediamine-tetra-acetate) have been used with varying success in treatment of this disease.[8] In 1956 Walshe[9] suggested penicillamine (β, β-dimethylcysteine), a degradation product of penicillin, as an effective copper chelating agent.

The purpose of this report is to present a family of which at least two members had clinically overt hepatolenticular degeneration (Figure 1), and to report copper metabolic studies in three generations of this family (Table 1). The results of extensive investigation of one severely ill member of the family and the therapeutic success obtained with penicillamine administered over a prolonged period are also described.

CASE REPORT

J. D., a 28-year-old lineman, was in good health until March, 1956 when he began having recurrent leg cramps. In January, 1957 he complained of jerkiness of the extremities, weakness of the legs, difficulty in talking, and dizziness. He was hospitalized briefly and diagnoses of acute labyrinthitis and psychoneurotic anxiety state were made. His clinical status deteriorated rapidly and severe tinnitus, dysphagia, dysarthria, ataxia, transient paraplegia, tremors, and weight loss became prominent features of his illness. He was completely bedridden and incapacitated when he was admitted to University Hospital on March 28, 1957.

His past medical history was noncontributory. The family pedigree is illustrated in Figure 1. A full male sibling (T. D.) died in his home at 28 years of age following a prolonged hospitalization for HLD. An adult male paternal cousin was said to have died of Parkinson's disease; further inquiry revealed that on post-mortem examination neuronal degeneration of basal ganglia, brain stem, and cerebellum was present. No other evidence of organic disease was observed. A younger brother (H. B. D.) is said to have had mild hepatitis but is now asymptomatic. No history suggestive of hepatic or neurologic disease in other members of this family was

uncovered, and there is no known consanguinity. The serum ceruloplasmin and copper levels in three generations of this family are shown in Table 1.

Physical examination revealed a poorly nourished but well developed white male. Classical Kayser-Fleischer rings were present grossly and on slit lamp examination. Ataxia, titubation of the head, asterixis, dystonia, nystagmus, left palpebral ptosis, right facial paresis, dysarthria, dysphagia, and slow cerebration were noted.

The hemogram, urinalysis, blood urea nitrogen, total and fractional serum protein, serum bilirubin, and inorganic phosphate levels were normal. Bromsulfalein retention was 20% in 45 minutes, cephalin-cholesterol flocculation was 3-plus at 24 hours, serum uric acid was 3.2 mg.%, and the serum calcium was 8.3 mg.%. The total serum copper level * varied from 40 to 49 μg.% (Table 1) and Ravin's test for serum copper oxidase [10] revealed abnormally low activity. Ceruloplasmin estimation * revealed complete absence of this copper protein in the serum (Table 1).

An 11-day course of therapy consisting of 3.96 gm. of BAL intramuscularly and 11 gm. of calcium versenate intravenously was administered to the patient without demonstrable improvement. During the following month he developed flexion contracture of the hand and wrist drop on the right, paresis of the right leg, and bilateral flexion contractures of his toes. His general condition rapidly deteriorated to the point of complete inability to speak or to eat. A second course of therapy consisting of 5.4 gm. of BAL intramuscularly and 30 gm. of calcium versenate intravenously

TABLE 2

Relationship of Penicillamine Dosage to the Renal Excretion of Copper by the Patient

Date	Penicillamine Dosage* (gm./24 hr.)	Urinary Copper Excretion (μg./24 hr.)
4-13-59	0	0
4-14-59	2.4	871
4-15-59	0	—
4-16-59	4.8	891
10-17-59	0	406
10-18-59	2.4	1354

* Continuous maintenance DL-penicillamine on alternate days, beginning August, 1957; not interrupted during urine copper studies (see text).

was given over a 15-day period. Although muscle relaxants were added to the regimen, no clinical improvement was noted and he was discharged June 11, 1957.

In June, 1957, 15 gm. of DL-penicillamine † were administered orally in daily divided doses over a two-week period without clinical improvement. In August, 1957 the prothrombin time was 47.5%. At this time penicillamine was resumed in a dosage of 0.3 gm. three times daily; the only apparent side effect of this medication was a generalized nonpruritic, papular skin eruption which subsided without discontinuing the therapy. The first definite clinical improvement was noted in October, 1957, four months after the start of penicillamine. There was evident a decrease in ataxia, drooling, tremors, and dysphagia. From this time on improvement was continuous and rapid. By April, 1958 the patient was able to go hunting and had actually shot a few wild rabbits. In June, 1958 the dosage of penicillamine was increased to 0.6 gm. four times daily on alternating days. Urinary copper excretion studies ‡ in relation to penicillamine dosage were carried out in April, 1959 and again in October, 1959 (Table 2).

* These determinations were performed by Dr. I. Herbert Scheinberg, Department of Medicine, Albert Einstein College of Medicine, New York, New York.

† DL-penicillamine was purchased from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin.

‡ These determinations were performed by Dr. I. Herbert Scheinberg, Department of Medicine, Albert Einstein College of Medicine, New York, New York.

By October, 1959 he had been talking clearly for two months and was able to drive an automobile, ride a bicycle, train hunting dogs, do electrical wiring and home gardening. He still had a slight intention tremor on the right, minimal asterixis, and sight facial weakness, and he still walked with an ataxic gait. Laboratory studies now revealed normal liver function with a prothrombin time of 80% and a bromsulfalein retention of 5.5%. The serum calcium was 10 mg.% and the serum uric acid was 2.9 mg.%. Slit lamp examination demonstrated markedly decreased Kayser-Fleischer rings.

At present he is working as a switchboard operator, and is maintained on a low copper diet, potassium sulfide 20 mg. three times daily, and the regimen of penicillamine described above.

Discussion

Prior to the use of powerful copper chelating agents in the treatment of hepatolenticular degeneration (HLD) the future of patients with this disease was considered hopeless. Since publication of the initial reports concerning the use of penicillamine as a "decoppering" agent in HLD,[7, 9] a marked change in the prognosis is becoming apparent. However, many of the clinical observations [11–17] concerning the use of this drug have been made on the basis of relatively short-term therapy. Only a small number of investigators [12, 15, 17] have reported their experiences in any appreciable detail following a prolonged clinical trial. The patient described in this communication has been receiving penicillamine for three and one-half years, and continues to maintain good health. In view of the startling therapeutic effects, greater emphasis should be placed on early detection of this genetically determined condition so that treatment may be started before irreversible tissue damage has occurred.

A careful examination of three generations of our patient's family was carried out. The family pedigree is shown in Figure 1. The total serum copper and ceruloplasmin levels of the patient's parents, surviving siblings, and children are shown in Table 1. Although abnormally low serum ceruloplasmin and copper levels have been detected in relatives of patients with HLD,[20, 21] in members of this family other than our patient these values were within normal limits; this finding is compatible with the autosomal recessive mode of inheritance described by Bearn.[3]

In our patient the symptoms were predominantly neurologic, and hepatic disease was not clinically evident, although laboratory studies revealed severe functional impairment of the liver. Classical Kayser-Fleischer rings were present and his course was acute and rapidly progressive, developing over a period of 12 months to complete incapacity. It is in this group of patients that therapy with British anti-lewisite (BAL) appears to be unsatisfactory in altering the course of the disease, a previous observation [7] supported by the patient presently reported. Indeed, it has been the experience of two groups that BAL, in some cases, may aggravate the course of the illness.[18, 19] In addition, the administration of BAL involves painful intramuscular injections and may result in severe toxic side effects.[16]

A comparison of 17 reported cases of HLD [7, 9, 12, 13, 14, 16] who received both BAL and penicillamine therapy is shown in Table 3. The majority, but not all, of these patients had a better cupruretic response to penicillamine than to BAL. The greater mean cupruretic response, two and one-half times that of BAL, and the ability to administer the compound indefinitely, with the consequent removal of more copper from the body, appear to be the principal advantages of penicillamine therapy.

The dramatic response of this patient to penicillamine therapy demonstrates the efficacy of its use in HLD and the results which may be obtained with prolonged treatment, even in the absence of an early initial response to the drug. It emphasizes the necessity for continuing the therapy despite the lack of a good clinical response during the first several months of treatment. The disappearance of neurologic involvement, detectable hepatic involvement, and Kayser-Fleischer rings which occurred in our patient has been noted previously.[17] The completeness of remission of the neurologic features in this case was both surprising and dramatic.

TABLE 3

Cupruretic Responses Compared in 17 Reported Cases Given Both BAL and Penicillamine

Drug	Dose Range* (mg./24 hr.)	Approximated Mean† and Range of Urinary Copper Excretion (μg./24 hr.)	Number of Cases Showing Greatest Cupruretic Response to Tested Drug
Control period		435 (84–880)	
BAL	80–400	1050 (137–2800)	3
Penicillamine	500–1500	2610 (500–4800)	14

* Drugs administered in short-term experiments in the majority of these cases.

† Mean of 24-hour urine collections, obtained from published tables or approximated from graph figures.[7,9,12,13,14,16] No attempt has been made to compare various laboratory analytical methods.

In order to demonstrate the relationship of penicillamine dosage to urinary copper excretion, total 24-hour urinary copper levels were estimated after varying doses of DL-penicillamine (Table 2). Optimal excretion was obtained on a daily dosage of 2.4 gm. DL-penicillamine administered orally in four divided doses. The absence of correlation, however, between clinical improvement and induced cupruresis has been observed by several investigators.[17, 22] No precise explanation, other than loss of excess tissue copper, of the therapeutic effect produced in this disorder by chelating agents of the monothiol (penicillamine) and of the dithiol (BAL) type, readily presents itself.

Although they are not usually severe enough to warrant discontinuing therapy, toxic reactions due to penicillamine, such as nausea and severe anorexia, transient erythematous rash, and Jacksonian convulsions have been reported.[15, 16] The patient in this report developed a generalized papular eruption during the early period of treatment which fortunately subsided without interruption of therapy.

Summary

1. A family pedigree is reported in which at least two members demonstrate hepatolenticular degeneration, and the total serum copper and ceruloplasmin levels in three generations of the family are presented.

2. Detailed studies were done on one of these patients who had relatively acute neurologic involvement and laboratory evidence of severe functional impairment of the liver. He responded dramatically to penicillamine given over a three-year period. DL-penicillamine in doses of 2.4 gm. given orally in four divided doses on alternate days appeared to be optimal in producing cupruresis in this patient.

3. A comparison of the acute cupruretic responses to BAL and penicillamine in 17 previously reported cases of hepatolenticular degeneration is presented.

Acknowledgments

The authors are indebted to Dr. Jolyon S. Tucker for referring this case and to Dr. Stephen J. Kelley for slit lamp examinations. The penicillamine was purchased by the State of Alabama Vocational Rehabilitation Service. The authors gratefully acknowledge the constant help of Miss Mary Sheffield in the study of this case and in the preparation of this manuscript.

Summario in Interlingua

1. Es reportate le arbore genealogic de un familia con al minus duo membros demonstrante degeneration hepatolenticular. Le valores del total cupro e ceruloplasmina del sero es presentate pro tres generationes del familia.

2. Esseva effectuate detaliate studios in un de iste patientes qui habeva relativemente acute implicationes neurologic e evidentia laboratorial de sever dysfunction del hepate. Ille respondeva dramaticamente a penicillamina administrate durante un periodo de tres annos. Un programma de DL-penicillamina in doses de 2,4 g per via oral in quatro partes, administrate omne secunde die, pareva esser le melio capace a inducer cuprurese in iste patiente.

3. Es presentate un comparation del acute responsas cupruretic a anti-lewisite britannic e a penicillamina in 17 previemente reportate casos de degeneration hepatolenticular.

BIBLIOGRAPHY

1. Wilson, S. A. K.: Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. **Brain 34**: 295, 1912.
2. Cartwright, G. E., Hodges, R. E., Gubler, C. J., Mahoney, J. P., Daum, K., Wintrobe, M. M., Bean, W. B.: Studies on copper metabolism. XIII. Hepatolenticular degeneration. J. Clin. Invest. **33**: 1487, 1954.

3. Bearn, A. G.: Genetic and biochemical aspects of Wilson's disease. Amer. J. Med. **15**: 442, 1953.
4. Anderson, P. J., Popper, H.: Changes in hepatic structure in Wilson's disease. Amer. J. Path. **36**: 483, 1960.
5. Warnock, C. G., Neill, D. W.: The diagnosis and treatment of Wilson's disease. Brain **81**: 258, 1958.
6. Bearn, A. G. *in* The metabolic basis of inherited disease, pp. 809–838. The McGraw-Hill Book Company, Inc., New York, 1960.
7. Bearn, A. G.: Wilson's disease: an inborn error of metabolism with multiple manifestations. Amer. J. Med. **22**: 747, 1957.
8. Bickel, H., Neale, F. C., Hall, G.: A clinical and biochemical study of hepatolenticular degeneration (Wilson's disease). Quart. J. Med. **26**: 527, 1957.
9. Walshe, J. M.: Penicillamine, a new oral therapy for Wilson's disease. Amer. J. Med. **21**: 487, 1956.
10. Ravin, H. A.: Rapid test for hepatolenticular degeneration. Lancet **1**: 726, 1956.
11. Ashby, M.: Hepatolenticular degeneration. Proc. Roy. Soc. Med. **50**: 884, 1957.
12. Fister, W. P., Boulding, J. E., Baker, R. A.: The treatment of hepatolenticular degeneration with penicillamine, with report of two cases. Canad. Med. Ass. J. **78**: 99, 1958.
13. Lawrie, N. R., Carter, R. A.: Acute case of Wilson's disease (hepatolenticular degeneration). Lancet **1**: 1309, 1958.
14. Cumings, J. N.: The treatment of hepatolenticular degeneration. Proc. Roy. Soc. Med. **52**: 62, 1958.
15. Seven, M. J., Kliman, B., Peterson, R. E.: Clinical studies with penicillamine in hepatolenticular degeneration. Amer. J. Med. Sci. **237**: 49, 1959.
16. Walshe, J. M.: Treatment of Wilson's disease with penicillamine. Lancet **1**: 188, 1960.
17. Scheinberg, I. H., Sternlieb, I.: The long term management of hepatolenticular degeneration (Wilson's disease). Amer. J. Med. **29**: 316, 1960.
18. Bearn, A. G.: The place of BAL in the therapy of Wilson's disease. Amer. J. Med. **21**: 134, 1956.
19. Hollister, L. E., Cull, V. L., Gonda, V. A., Kolb, F. O.: Hepatolenticular degeneration. Clinical, biochemical and pathologic study of a patient with fulminant course aggravated by treatment with BAL and Versenate. Amer. J. Med. **28**: 623, 1960.
20. Neale, F. C., Fischer-Williams, M.: Copper metabolism in normal adults and in clinically normal relatives of patients with Wilson's disease. J. Clin. Path. **11**: 441, 1958.
21. Cartwright, G. E., Markowitz, H., Shields, G. S., Wintrobe, M. M.: Studies on copper metabolism. XXIX. A critical analysis of serum copper and ceruloplasmin concentrations in normal subjects, patients with Wilson's disease and relatives of patients with Wilson's disease. Amer. J. Med. **28**: 555, 1960.
22. Walshe, J. M.: Current views on the pathogenesis and treatment of Wilson's disease. Arch. Intern. Med. **103**: 155, 1959.

THE ORIGIN AND NATURE OF ANISOTROPIC URINARY LIPIDS IN THE NEPROTIC SYNDROME * †

By JAMES G. ZIMMER, M.D., RICHARD DEWEY, M.D., CHRISTINE WATERHOUSE, M.D., F.A.C.P., and ROGER TERRY, M.D.,
Rochester, New York

INTRODUCTION

ANISOTROPIC lipid material has been observed in the urine sediment of patients with the nephrotic syndrome since the early 1900s. These globular anisotropic bodies have the well known "Maltese cross" appearance when viewed with a polarizing microscope. This appearance of certain spherical bodies in a liquid medium has caused them to be classified, since about 1905, as "fluid spherocrystals" or "spherulites," and they are felt to be pure crystalline substances in a phase intermediate between the fluid and the crystalline states.[1]

Most of the studies concerning the localization and chemical nature of anisotropic lipids are to be found in the older literature. In 1858 Mettenheimer [2] observed "Maltese cross" birefringence in liquid expressed from the adrenals. Subsequently this has been observed in nerve myelin and in material from various pathologic conditions, including inflammatory and neoplastic,[3] and especially in atheromata. Munck [4] first established the constant clinical relationship of the anisotropic bodies in urine sediments to the "lipoid degeneration" found in the kidneys of patients with the nephrotic syndrome. He felt this "lipoid degeneration" characterized by birefringence occurred only in irreversibly degenerating cells and should be contrasted to the usual fatty degeneration. The chemical nature of the anisotropic material has never been directly studied. It is felt to be lipid in nature, since it is unchanged by protein destroying substances.[5] Adami [6] found that morphologically similar "Maltese cross" bodies could be produced artificially from cholesterol esters, but not from other lipid materials. One other piece of indirect evidence is given by the work of Windaus,[7] who found an increase

* Received for publication July 5, 1960.

From the Departments of Medicine and Pathology, University of Rochester School of Medicine and Dentistry, Rochester New York.

Drs. Zimmer and Dewey are Associate Residents and Assistants in Medicine; Dr. Waterhouse is Associate Professor of Medicine; and Dr. Terry is Associate Professor of Pathology; University of Rochester School of Medicine and Dentistry, Rochester, New York.

† This study was aided by Grant P-138 from the American Cancer Society, and by the Ernest L. Woodward Fund.

Requests for reprints should be addressed to Christine Waterhouse, M.D., Associate Professor of Medicine, University of Rochester School of Medicine and Dentistry, 260 Crittenden Boulevard, Rochester 20, New York.

in cholesterol esters of kidneys which contained anisotropic material pathologically, but no increase in free cholesterol. The anisotropic material in kidneys has been observed largely in the tubular cells, mainly those of the proximal tubules.[8-11]

Since there seemed to be no direct evidence bearing on the chemical nature of the anisotropic lipid material in the urine and in the tubules of patients with the nephrotic syndrome, or on the origin and mode of excretion of these lipids, it was felt that further investigation of the problem was warranted, using more recently developed and applicable technics.

Methods

Histologic: Frozen sections of renal biopsy material from several patients with the nephrotic syndrome were stained with Oil Red O and Sudan Black lipid stains. These frozen sections, as well as the urine sediments, were examined under polarized light.

Fig. 1. Anisotropic "Maltese cross" bodies seen under polarized light, concentrated by flotation from centrifuged urine sediment of a patient with nephrotic syndrome. 104 ×.

Chemical Analysis of the Anisotropic "Maltese Cross" Bodies: Eleven 24-hour urine specimens were collected from four patients with nephrotic syndromes of various etiologies. They all contained large numbers of the anisotropic bodies which it was possible to concentrate by flotation at the meniscus when the sediment was centrifuged in hypertonic sucrose (0.88M) or, in some cases, in the urine itself (Figure 1). The concentrated "Maltese cross" bodies appeared to be free of other particulate matter when examined under a polarizing microscope. An approximate volumetric equivalent of the liquid upon which the anisotropic material floated and which contained

essentially no anisotropic material was used as a control and treated in the same way. The material was extracted in 50% methanol in chloroform, dried with benzene, re-extracted in chloroform, and chromatographed on silicic acid paper in a 96:6 ratio of N-heptane and 2,4-dimethyl-4-heptanone. The papers were stained with rhodamine G for all the lipid fractions, and with phosphomolybdic acid, which is specific for cholesterol in the free or esterified form. Two specimens were also chromatographed on silicic acid columns as prepared by the method of Marinetti et al.[12] and the cholesterol in the cholesterol ester and free cholesterol fractions was quantitated by the Liebermann-Burchard color reaction.[13]

Study of Mode of Excretion of Cholesterol Esters: A dose of I^{131}-labeled triolein was administered orally to two patients with the nephrotic syndrome. Although the exact site of labeling is unknown, serum cholesterol esters become labeled during the first 12-hour period following such administration and their specific activity then decreases over the next 12 hours. Two successive 12-hour urine specimens were collected following the triolein administration and the sediment of each was separated from the urine. Lyophilized aliquots of both the urine specimens and the two separated sediments were extracted in chloroform, and the cholesterol ester fraction of each of the four specimens was eluted from silicic acid columns with petroleum ether. The radioactivity of the cholesterol ester fraction was counted with a well type sodium iodide scintillation crystal and a standard scaler, and the fraction was quantitated by the Liebermann-Burchard color reaction. The specific activity of each specimen was calculated as the number of counts per minute per 10 μg. of cholesterol.

FIG. 2. Urine sediment from a patient with nephrotic syndrome; under polarized light. 104 ×.

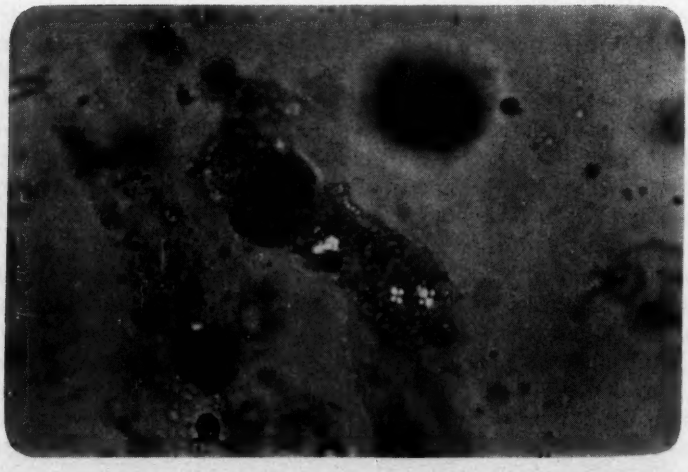


FIG. 3. Tubular cast in nephrotic syndrome; under polarized light. 363 ×.

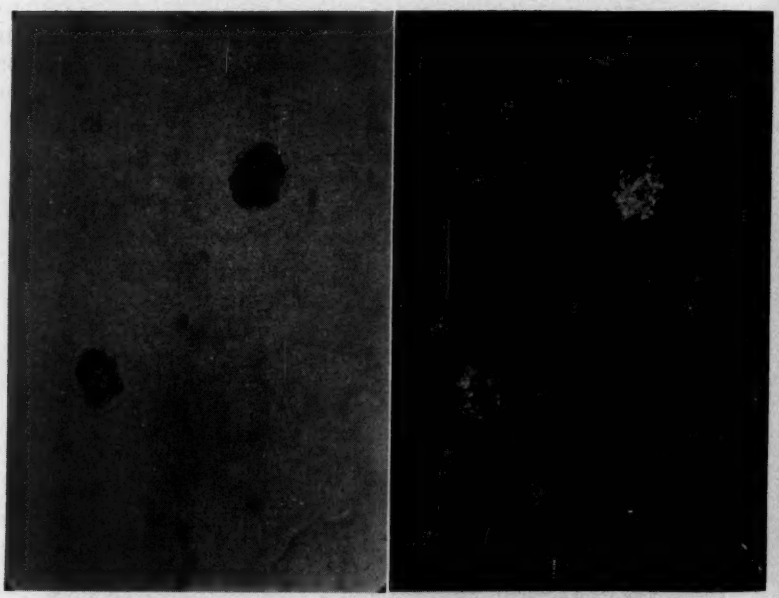


FIG. 4 (Left). "Oval fat bodies" in urine sediment of patient with nephrotic syndrome. Note the membrane surrounding the clump of globules. 188 ×.
FIG. 5 (Right). The same field as in Fig. 4; under polarized light. 188 ×.

Results

Histologic: The urine sediments of the patients studied contained large numbers of "Maltese cross" spherules, some of which were seen within tubular casts (Figures 2, 3). The so-called "oval fat bodies" described by Addis[14] were observed and found generally to be composed of aggregations of the Maltese cross bodies within what appeared to be a cellular membrane, as described before[15] (Figures 4, 5). The frozen sections from biopsy, stained with lipophilic stains, showed large amounts of lipid material within

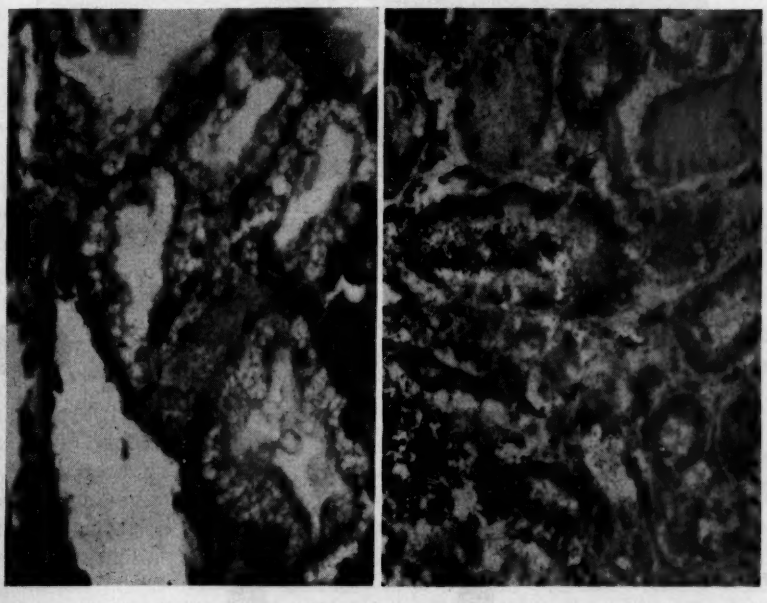


Fig. 6 (Left). Section of renal biopsy from patient with nephrotic syndrome, stained with hematoxylin and eosin, showing the typical vacuolated areas in the tubular cells where lipid has been dissolved during preparation. 160 ×.

Fig. 7 (Right). Frozen section of renal biopsy from a patient with nephrotic syndrome, stained with Oil Red O lipid stain, showing large amount of lipid material (black) within the tubular cells. (Normal tubules contain no stainable lipid.) 104 ×.

the tubular cells, and much smaller amounts were seen in the interstitium and even in some glomeruli (Figure 7). Those sections examined with polarized light alone showed anisotropic material within the tubular cells, some of which had the "Maltese cross" appearance (Figure 8). There was considerably less anisotropic material than stainable lipid material, indicating that not all of the lipid was anisotropic. Also notable, as observed before,[8] was the fact that only certain nephrons appeared to be involved with the lipid inclusions.

FIG. 8. Frozen section of renal biopsy from a patient with nephrotic syndrome, seen under polarized light, showing anisotropic material in the tubular cells, some of which have the "Maltese cross" appearance. 104 ×.

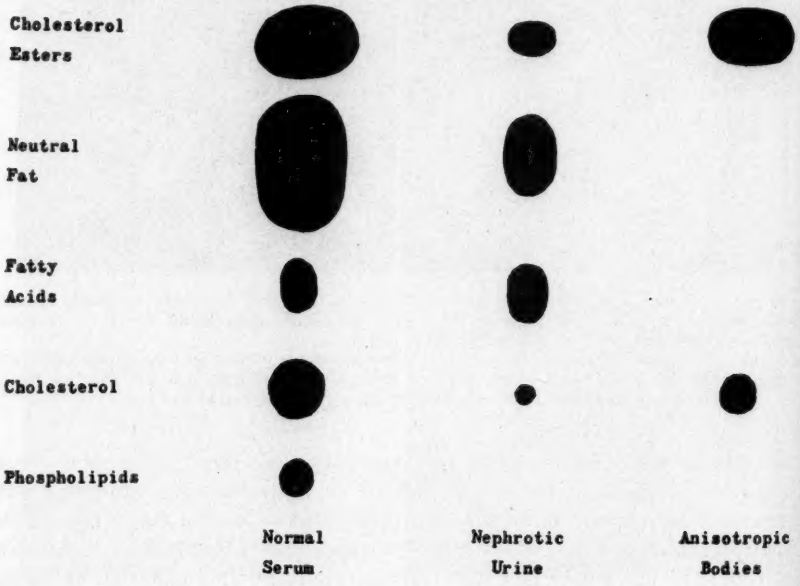


FIG. 9. Graphic representation of lipids by paper chromatography of the anisotropic "Maltese cross" bodies in urine sediment in nephrotic syndrome, compared with normal serum lipids and lipids in solution in urine of nephrotic patients.

TABLE 1

Relative Proportions of Cholesterol Ester and Free Cholesterol in the Anisotropic "Maltese Cross" Bodies, as Obtained by Column Chromatography

Patient	Cholesterol Esters (μg. of cholesterol)	Unesterified Cholesterol (μg.)
1	32	0
2	70	28

Chemical Analysis: By silicic acid paper chromatography, cholesterol esters and free cholesterol were found in the specimens of concentrated anisotropic Maltese cross bodies; the cholesterol esters were found in considerably greater quantity, as seen by phosphomolybdic acid stain (Figure 9). Neutral fat, free fatty acids, and phospholipids were either not present at all in the concentrated anisotropic bodies, or were present in amounts only equivalent to or less than those found in the control liquid which contained only lipids in solution, presumably as lipoprotein.

The chemical quantitation of the cholesterol ester and free cholesterol fractions of the concentrated anisotropic material by the Liebermann-Burchard reaction confirmed the predominance of cholesterol ester over free cholesterol. In one specimen there were 70 μg. of cholesterol in the cholesterol ester fraction and 28 μg. in the free cholesterol fraction. (The ratio by weight of cholesterol ester to free cholesterol would therefore be even greater.) In the other specimen there were 32 μg. of cholesterol in the cholesterol ester fraction and none in the free cholesterol fraction (Table 1). Thus the Maltese cross bodies, according to these determinations, contain predominantly cholesterol ester, with a smaller amount of free cholesterol also being present.

Study of Mode of Excretion: In the tracer study, the labeled cholesterol ester in solution in the urine, as measured by specific activity, decreased over the 24-hour period in the same fashion as did that in the serum. In one patient, the specific activity fell from 33 cpm./10 μg. cholesterol in the first 12-hour period to 1.1 cpm. in the second 12-hour period. In the other patient, it decreased from 146 to 72 cpm. (Table 2). However, the labeled cholesterol ester in the sediment which contained the anisotropic material increased between the two 12-hour periods, going from a specific activity

TABLE 2

Specific Activity of the Cholesterol Ester Fraction from Nephrotic Urine, Following I^{131}-labeled Triolein Ingestion

Patient	Fraction	First 12 Hours (cpm./10 μg. cholesterol)	Second 12 Hours (cpm./10 μg. cholesterol)
1	Supernatant	33.0	1.1
	Sediment	1.1	6.3
2	Supernatant	146.0	72.0
	Sediment	0	38.0

of 1.1 to 6.3 in one patient, and from 0 to 38 in the other. Thus, there is a delay in the excretion of the sedimented particles containing labeled cholesterol ester as compared with the cholesterol ester in solution. This finding implies that the cholesterol esters in solution, probably as lipoprotein, are simply filtered through the damaged glomerulus into the urine directly, while the particulate cholesterol ester in the sediment is delayed in the tubular cells before reëxcretion.

Discussion

A tentative reconstruction of the events in the abnormal renal accumulation of lipids and their excretion in the urine of patients with the nephrotic syndrome can be presented. It is based on the present evidence concerning cholesterol ester, but it is likely that the same pattern may also obtain in the case of the other lipid elements.

Lipoprotein is lost through damaged glomeruli, as was demonstrated by Schradl et al. in patients with proteinuria of any etiology.[16] Part of this filtered lipoprotein is then reabsorbed by the tubular cells. The possibility that some of the lipid found in the tubules and in the urine is obtained directly from the blood without being filtered through the glomerulus is not entirely excluded. However, experiments with amphibians indicate that glomerular damage is necessary before cholesterol can enter the urine,[17, 18] and in dogs with alimentary hypercholesterolemia there is no cholesteroluria until a renal lesion (presumably glomerular) is produced with uranium nitrate.[19, 20] In human beings there is apparently no experimental evidence available, but certainly the hypercholesterolemic state alone is not sufficient to produce either the "lipoid" tubular changes or the abnormal amounts of urinary lipids. It appears therefore that a glomerular "leak" of lipoprotein is probably necessary before appreciable lipid appears in the tubules or in the urine.

The reabsorption of part of the filtered lipoprotein by the tubular cells may be comparable to the process occurring normally in amphibians possessing an "open nephron" system.[17, 18] The proximal part of the tubule in that type of nephron has a connection with the peritoneal cavity. Therefore reabsorption of protein and lipoprotein by the proximal tubular cells from the peritoneal fluid is mandatory to prevent loss and depletion. This tubular function, called "athrocytosis," probably occurs to some extent normally in mammals. If it does occur in greater degree in persons with the nephrotic syndrome, it may not imply true metabolic dysfunction resulting in degeneration of the tubular cells. However, at least as is shown by human aortic cell tissue culture, excessive intracellular cholesterol causes cell death.[21]

Some of the lipoprotein which enters the tubular cells is altered—in the case of the cholesterol ester to an anisotropic state—probably thereby losing its protein complex. This then re-enters the urine, either as material ex-

truded from cells or as sloughing tubular cells which may appear as the oval fat bodies. This altered material, which is found as particulate lipid matter in the sediment, appears later than does the lipoprotein coming directly from the glomerular filtrate, as was demonstrated in the labeling experiment. The anisotropic "liquid crystalline" material, which is composed largely of cholesterol ester with a smaller component of free cholesterol, appears in the urine sediment as the "Maltese cross" bodies.

Summary

The anisotropic lipid material in urine from patients with the nephrotic syndrome, in the form of "Maltese cross" spherulites, is apparently composed largely of cholesterol ester with a smaller component of free cholesterol. The labeled cholesterol ester in the urine sediment appeared more slowly than did the labeled cholesterol ester in solution (probably as lipoprotein). These findings suggest that the cholesterol esters, and possibly other lipids, are lost through the damaged glomerulus, are partly reabsorbed by the tubular cells, and are then re-extruded in a particulate form. Thus two distinct lipid phases appear in the urine—one a lipoprotein form in solution from the glomerular filtrate, and one a particulate form in the sediment arising from tubular cells.

Summario in Interlingua

Iste studio concerne le natura chimic del anisotropic material lipidic in le urina e in le tubulos de patientes con le syndrome nephrotic. Es etiam presentate observationes relative al origine e al modo de excretion de ille lipidos. Le material anisotropic in le urina esseva concentrate per medio de methodos de flottation, e postea le lipidos esseva extrahite e separate per chromatographia a acido silicic. Le lipido predominante trovate in iste material esseva estere cholesterolic, sed micre quantitates de cholesterol libere esseva etiam uniformemente incontrate. Quantitates traciatori de trioleina marcate con I^{131} esseva administrate a duo patientes con le syndrome nephrotic. Le esteres cholesterolic del sero attingeva alora lor plus alte nivello de radioactivitate specific post un intervallo de 12 horas. Specimens de urina esseva colligite ab le duo patientes, e le activitate specific del estere cholesterolic esseva determinate in le urina mesme e in le sedimentos urinari. Esseva trovate que le activitate specific de estere cholesterolic in le solubile lipoproteinas del urina sequeva satis strictemente le activitate specific del estere cholesterolic in le sero. Tamen, le activitate specific del estere cholesterolic in le sedimento ab le specimens de urina monstrava un augmento tardive. Isto significa que reabsorption e alteration habeva occurrite in le cellulas tubular pro producer iste typo particular de lipido in le urina.

BIBLIOGRAPHY

1. Schenck: Flüssige Kritalle, Leipzig, 1905.
2. Mettenheimer: Correspondence in Bl. d. Verein. F. ges. Arb. z. Förder. d. Wissensch. Heilk **31**: 467, 1858.
3. Stengel, A., Austin, J. H.: Syphilitic nephritis. Amer. J. Med. Sci. **149**: 12, 1915.

4. Munck, F.: a) Über lipoide Degeneration. Virchows Arch. **194**: 527, 1908; b) Klinische Diagnostik der degenerativen Nierenerkrankungen. Z. Klin. Med. **78**: 1, 1913; c) Die Nephrosen. Med. Klinik **12**: pp. 1019, 1047, 1073, 1916.
5. Brice, A. T., Jr.: The incidence of lipoids in urine. J. Lab. Clin. Med. **15**: 953, 1930.
6. Adami, J. G.: The myelins and potential fluid crystalline bodies of the organism. J. A. M. A. **48**: 463, 1907.
7. Windaus, A.: Über die quantitative Bestimmung des Cholesterins und des Cholesterinester in einigen normales und pathologischen Nieren. Z. Physiol. Chemie **65**: 110, 1910.
8. Dunn, I. S.: Nephrosis or nephritis? J. Path. Bact. **39**: 1, 1934.
9. Leiter, L.: Nephrosis. Medicine **10**: 135, 1931.
10. Oliver, J.: New directions in renal morphology: a method, its results and its future. Harvey Lectures **40**: 102, 1944–45.
11. Allen, A. C.: The clinicopathologic meaning of the nephrotic syndrome. Amer. J. Med. **18**: 277, 1955.
12. Marinetti, G. V., Erbland, J., Kochen, J.: Quantitative chromatography of phosphatides. Fed. Proc. **16**: 837, 1957.
13. Burchard, H.: Beiträge zur Kenntniss der Cholesterine (dissertation, 26 pp.), Rostock, Germany, 1889.
14. Addis, T. F.: Glomerular Nephritis, pp. 207–208, The Macmillan Co., N. Y., 1948.
15. Quinn, J. R., Zimmerman, H. J.: Significance of oval fat bodies in urinary sediment. Amer. J. Clin. Path. **24**: 787, 1954.
16. Schradl, W., Böhle, E., Becker, G.: Über die Ausscheidung von Lipoprotein im Urin bei den sogenannten Albuminurien. Deut. Arch. Klin. Med. **202**: 415, 1955–56.
17. Gerard, P.: Histopathology of the vertebrate nephron. J. Anat. **70**: 354, 1935–36.
18. Smetana, H., Johnson, F. R.: The origin of colloid and lipoid droplets in the epithelial cells of the renal tubules. Amer. J. Path. **18**: 1029, 1942.
19. Weltmann, O., Biach, P.: Zur Frage der experimentellen Cholesteatose. Z. exper. Path. und Therap. **14**: 367, 1913.
20. Genck, M.: Über das vorkommen und die bedeutung droppelbrechender Substangen im Ham. Deut. Arch. Klin. Med. **125**: 333, 1918.
21. Rutstein, D. D., Ingenito, E. F., Craig, J. M., Martinelli, M.: Effects of linoleic and stearic acids on cholesterol-induced lipoid deposition in human aortic cells in tissue culture. Lancet **1**: 545, 1958.

ERRATUM

In Table 1 of the paper entitled "The Effect of Thiazide Diuretics on the Abnormal Kidney," by Drs. Dreifus, Duarte, Kodama, and Moyer, Vol. 53, pp. 1172–1173, December, 1960, the column entitled "Potassium Excretion" (11th from the left) should read μEq./min., and the column entitled "Solute Excretion" (12th from the left) should be deleted.

RENAL MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS; A CLINICAL AND PATHOLOGIC STUDY OF 90 CASES * †

By Louis J. Soffer, M.D., F.A.C.P., A. Louis Southren, M.D.,‡ H. E. Weiner, M.D., and R. L. Wolf, M.D., *New York, N. Y.*

The present report is concerned with a study of the renal manifestations in 90 patients with systemic lupus erythematosus who were seen at the Mount Sinai Hospital from 1949 to 1959. The role of various factors in the pathogenesis of the renal disease is examined. Consideration is given to a correlation between the clinical and laboratory evidence of renal damage and the histologic study of kidney tissue. An attempt has been made to determine the value of corticotropin and the glucogenic steroids in the management of the renal complications. Only those cases are included which demonstrated characteristic clinical and laboratory evidence of systemic lupus erythematosus, in addition to the presence of one or more positive cell tests for the disease. Because the initial symptoms were frequently vague and nonspecific, it was decided to date the onset of the disease as the time a positive diagnosis was established, usually the first hospital admission. The minimal criterion for renal involvement was the presence of a persistent albuminuria, although almost all patients showed, in addition, hematuria, casts, and other abnormalities in several renal function studies. In 19 cases pathologic specimens of the kidney were available. Twelve were obtained through renal biopsy and seven from post-mortem examination.

Results

Tables 1 and 2 list the sex, race, and age distribution of the 90 patients.

Sex: Although acute disseminated lupus erythematosus is a disease predominantly seen in females it does occur in the male. Twelve per cent of our group are males, and this percentage corresponds quite well to the 15 to 20% incidence reported in the literature.

Race: There were eight Negro and six Puerto Rican patients in our

* Received for publication June 16, 1960.

From the Endocrine Research Laboratory and Clinic of the Department of Medicine of the Mount Sinai Hospital, New York, N. Y.

† Aided by Grant A-921 from the National Institutes of Health.

‡ Present address: The Jewish Hospital of Brooklyn, Brooklyn, N. Y.

We are indebted to the Schering Corporation for the generous supply of Meticortelone and Meticorten; to the Upjohn Company for Medrol; to Wyeth Laboratories for Bicillin; and to the Lederle Laboratories for gamma globulin.

Requests for reprints should be addressed to Louis J. Soffer, M.D., Attending Physician and Head of Endocrinology, Mount Sinai Hospital, Fifth Avenue and One Hundredth St., New York 29, New York.

TABLE 1
Sex and Race Distribution

	With Renal Involvement	Without Renal Involvement	Total
Sex			
Male	6	5	11
Female	50	29	79
Race			
White	47	29	76
Negro	6	2	8
Puerto Rican	3	3	6
Total Patients	56	34	90

series. Their general clinical manifestations are indistinguishable from those seen in the white patients.

Age: The youngest patient was six years of age. The oldest was a man of 70. The disease occurred most frequently, however, between the ages of 15 and 30 years.

There appeared to be an inverse correlation between the incidence of renal involvement and the age of the patient. Of 53 patients with renal involvement at the time the initial diagnosis was established, 32 (61%) were under 30 years of age. In addition, three patients developed renal damage subsequent to the first hospital admission (Table 3), all of them under 21 years of age. Of the 34 subjects without renal injury 22 (65%) were over 30 years old.

Kidney disease was apparently more severe in the younger age group. Of 34 patients with renal involvement under 30 years of age, 16 have died, 12 have azotemia, and six have relatively minor renal involvement. Of 21 patients over 30 years of age, eight have died, four have azotemia, and nine have minor involvement.

TABLE 2
Age at First Hospital Admission

Age (yrs.)	With Renal Involvement	Without Renal Involvement	Total Patients
0–9	1	0	1
10–19	15	6	21
20–29	19	6	25
30–39	11	10	21
40–49	6	7	13
50–59	3	3	6
Over 60	1	2	3

Familial Incidence: There are two families in our group in which systemic lupus erythematosus has occurred in two siblings of each family. Such familial incidence has been described before.[1] It is interesting to note that the clinical manifestations of the disease in the paired siblings may vary considerably. In one pair of sisters aged 11 and 13 years, the 11-year-old child developed a fulminating acute disseminated lupus erythematosus which was associated with early severe renal failure and death several weeks after the onset. In the 13-year-old sibling, the essential manifestations were those of recurrent moderate fever, arthralgias, and a mild facial eruption. This child, now 20, has not developed any evidence of renal injury. The other couple are a sister and brother, aged 23 and 25 years, respectively. The sister has had episodes of fever, a facial rash, and evidence of renal involvement. In the brother, the major clinical manifestation of the illness has been moderate joint pains.

Onset of Renal Disease: Those patients who had impairment of renal function generally manifested it early in the course of the illness. The longer the disease continued without the development of this complication,

TABLE 3

Onset of Renal Involvement in Relation to Time of First Hospital Admission

	Number	Per Cent
Present on first hospital admission	53	94%
Absent on first hospital admission but present within one year of that admission	2	4%
Absent until more than one year after first hospital admission	1	2%
Total	56	100%

the less likely was it to occur. Of the 56 patients with renal lesions, 53 already had this complication at the time of the initial hospital admission (Table 3). In three patients the onset of renal involvement occurred subsequent to the first hospital admission, in two patients within one year, and in one within three years.

Clinical Considerations: Table 4 lists the incidence of hypertension, edema, and fundal abnormalities in patients with and without renal involvement. Although hypertension occurred more commonly in those with renal impairment, it was present in less than 50% of this group. Only two patients in the group without renal involvement showed a significant elevation of blood pressure.

Edema was present in 18 patients with renal lesions. None of the patients without kidney damage developed this complication. The edema varied considerably in severity and involved the ankles in nine, the periorbital areas in five, and was diffuse in four instances. Fourteen had an associated hypoalbuminemia. Of the 18 subjects with renal damage and edema the mean serum albumin was 2.3 gm.%, as compared to 2.9 gm.%

TABLE 4
Clinical Manifestations*

Manifestation	With Renal Involvement		Without Renal Involvement	
	Number	% (of those with renal disease)	Number	% (of those without renal disease)
Blood pressure above 140/90 mm. Hg	24 (55)	44%	2 (34)	6%
Edema present	18 (52)	35%	0 (34)	0%
Abnormal fundi	16 (53)	30%	3 (34)	9%

* Number in parenthesis is the number of patients in which the presence or absence of the manifestation is known.

in the 24 patients without edema. Twelve of the latter 24 patients had normal serum albumin levels. Edema was found to be a poor prognostic sign. Twelve of the 18 patients with renal involvement and edema have died, as compared to 12 of 38 patients with renal involvement unassociated with this finding.

Fundal abnormalities were present in 16 cases with renal involvement. All had hypertension. The degree of fundal change varied considerably in the group. The mortality incidence in the patients with renal damage and with fundal changes was not significantly different from the mortality seen in those with renal impairment without such abnormalities. Three of 34 patients without renal injury showed minor changes. In one patient this was accounted for by an associated hypertension; in the other two the fundal abnormalities consisted of increased tortuosity of the arterioles.

There were 16 patients with a nephrotic syndrome (Table 5). Of these, seven had clinical and laboratory evidence of nephrosis at the time of the initial hospital admission. These findings included edema, marked proteinuria, hypoalbuminemia, hypercholesterolemia, and an abnormal urinary sediment. Three additional patients developed nephrosis subsequent to the

TABLE 5
The Duration of Survival in Nephrosis in Relation to the Presence or Absence of Hypercholesterolemia

Mode of Presentation	Number of Patients	Number Died	Mean Survival After Onset of Nephrotic Syndrome
Nephrotic syndrome with hypercholesterolemia	10*	8	8 months
Nephrotic syndrome without hypercholesterolemia	6†	2	1 month

* 2 lost to follow-up.
† 1 lost to follow-up.

TABLE 6

Urinary Findings in Patients with Renal Involvement*

Manifestation	Number in which Present	Per Cent
Albuminuria	56 (56)	100%
Hematuria	49 (55)	88%
Pyuria	34 (55)	63%
Casts	38 (55)	70%

* Number in parenthesis is the number of patients in which the test was done.

first hospital admission, two within three years and one within six years. Four patients presented with all the criteria of the nephrotic syndrome with the exception of a serum cholesterol level within the normal range. In two additional cases the normocholesterolemic variant of the nephrotic syndrome became evident approximately six years after the initial hospitalization.

The nephrotic syndrome when associated with hypercholesterolemia was found to be of graver import than was the similar complication in patients with normal serum cholesterol levels (Table 5). Five patients in the former category succumbed to the illness within two years of onset, with a mean survival of nine months. The three patients who developed nephrosis subsequent to the initial observation all died within six months. The average survival for both groups was eight months. The six subjects with the normocholesterolemic variety fared somewhat better. Three are still alive one to three years after the onset of nephrosis.

TABLE 7

Kidney Function Tests

Test	No. of Patients Studied		Mean	Maximum	Minimum	No. of Patients in Which Values Were Abnormal	
						Number	Per Cent
Phenolsulphonphthalein excretion in 15 min.*	With R.I.†	21	16	35	0	13	62
	Without R.I.	14	36	65	10	1	7
Phenolsulphonphthalein excretion in 2 hrs.*	With R.I.	26	56	90	20	9	35
	Without R.I.	19	73	100	40	3	16
Creatinine clearance, c.c./min.*	With R.I.	9	45	85	12	8	89
	Without R.I.	3	86	99	54.5	1	33
Urinary concentration test*	With R.I.	18	1.017	1.040	1.006	5	28
	Without R.I.	14	1.024	1.032	1.016	1	7
Blood urea nitrogen*	With R.I.	38	70	266	8	26	68
	Without R.I.	24	14	20	9	0	0

* Normal values:
15-min. phenolsulphonphthalein >25%
2-hr. phenolsulphonphthalein >50%
Creatinine clearance >80 cc./min.
Urinary concentration test > 1.022
Blood urea nitrogen <22 mg.%

† R.I. = renal involvement.

Renal Function Studies: The patients with renal lesions all had persistent albuminuria, 88% had hematuria, 63% had pyuria, and 70% had casts in the urinary sediment (Table 6).

Renal function studies, including phenolsulphonphthalein excretion, urine concentration, blood urea nitrogen, and creatinine clearance were done in more than half of the group, usually at the initial hospital observation (Table 7). The 15-minute excretion of phenolsulphonphthalein and the creatinine clearance test yielded the most useful information in terms of appraisal of renal status. Among the patients with renal damage a significantly decreased phenolsulphonphthalein excretion was present in 62% after 15 minutes, as compared to 35% after two hours. The creatinine

TABLE 8
Laboratory Data*

Manifestation	With R.I.		Without R.I.	
	No.	%	No.	%
Anemia†	44 (54)	81	19 (34)	56
Total protein less than 6.5 gm.%	24 (50)	48	4 (25)	16
Total albumin less than 3 gm.%	33 (50)	66	4 (25)	16
Total globulin more than 4 gm.%	12 (50)	24	8 (26)	31
Abnormal serum electrophoresis				
Increased gamma globulin	9 (18)	50	10 (10)	100
Other abnormalities	8 (18)	45	5 (10)	50
Throat culture with beta-hemolytic streptococcus	1 (11)	9	1 (4)	25
ASO titer more than 100	6 (18)	33	1 (8)	12.5
CRP 1-plus or greater	5 (14)	36	2 (5)	40

* Number in parenthesis is the number of cases studied.
† Hemoglobin less than 12 gm.%.
‡ R.I. = renal involvement.

clearance was below normal in almost all patients who had impairment of renal function. In two of these cases the creatinine clearance was markedly reduced early in the course of renal involvement although the other measures of renal function were only slightly decreased. Both patients died within two years of the first hospitalization.

The urine concentrating ability proved to be the least sensitive of the renal function tests. Only 28% of the patients with renal impairment showed an abnormal urine concentrating ability. The blood urea nitrogen was eventually elevated in 68% of the patients with renal involvement.

Additional Laboratory Data: Additional laboratory results are shown in Table 8. Anemia was present in 81% of the patients with renal damage

and in 56% of those without such complications. The anemia varied in severity and was usually of the normochromic, normocytic type; it was unresponsive to iron therapy. A clinically demonstrable hemolytic anemia was present in four patients, two with and two without renal disease. However, a positive Coombs test was present in 10 additional subjects.

Hypoproteinemia was frequently encountered in patients with renal involvement. The decrease in total protein was due primarily to a reduction in the serum albumin fraction. However, hypoalbuminemia was also found in four patients without renal injury. In contrast to the infrequency with which hypoalbuminemia was present in patients without renal impairment, hyperglobulinemia occurred with equal incidence in both groups.

TABLE 9
The Relation Between the Degree of Histologic Damage, Clinical Data, and Renal Function Abnormalities in 19 Patients*

Renal Damage on Basis of Renal Histology	Number of Cases	Hypertension (>140/90) mm. Hg	Edema	Elevated Blood Urea Nitrogen†	Persistent Urine Abnormalities	Decreased Phenolsulphonphthalein Excretion		Abnormal Concentration Test†	Number Died
						15 Min.†	2 Hrs.†		
0	1	1	0	0	0	0	0	0	0
1+	2	0	0	0	0	0 (1)	0 (1)	0 (1)	0
2+	9	4	5	6	9	1 (5)	3 (6)	1 (4)	5
3+	4	1	2	2	4	2 (3)	1 (3)	0	1
4+	3	1	2	3	3	2	0	1 (1)	2

* Number in parenthesis is the number of patients in whom the test was performed.
† Normal values:

Blood urea nitrogen	<22 mg.%
15-min. phenolsulphonphthalein	>25%
2-hr. phenolsulphonphthalein	>50%
Urinary concentration test	> 1.022

Abnormal serum electrophoretic patterns were equally common in patients with and without renal lesions. The usual electrophoretic abnormality consisted of an increase in the gamma globulin fraction, although this occurred with greater frequency in the patients without renal damage. However, significant reductions in the serum gamma globulin levels were often present in subjects with severe renal disease. An increase in the $alpha_2$ globulin occurred often in both groups.

Bacteriologic Studies: In an investigation of the possible role of beta-hemolytic streptococcus infection in renal involvement, throat flora were cultured on one or more occasions in 10 patients with renal impairment during the course of the illness. In only one instance was a positive throat culture obtained. This was associated with a moderate elevation of the antistreptolysin O titer. An increase in the antistreptolysin O titer without a positive throat culture for beta-hemolytic streptococcus was found in three

additional patients with renal disease. Vigorous and prolonged penicillin therapy failed to alter the progression of the renal complication.

Correlations Between the Laboratory Data and Renal Histologic Study: The relationship between the structural changes in the kidney and renal function as determined by various laboratory procedures was studied in 19 patients. Renal tissue was obtained by renal biopsy in 12, and from post-mortem examination in seven cases. Each specimen was graded from 0 (normal) to 4-plus (marked) according to the over-all severity of the histologic changes.

As is seen in Table 9, the urinalysis was normal in three of the group. In one of the three the renal biopsy was histologically normal and in the other two there was a mild glomerulitis. These patients have now been free of clinical evidence of renal involvement for three years. In 16 other cases the urinalysis was consistently abnormal. In each case renal damage was present on histologic examination. The more severe renal changes were associated with an increase in proteinuria and larger numbers of cellular elements in the urinary sediment. Four patients with advanced renal impairment manifested clinical and laboratory evidence of nephrosis, including hypercholesterolemia. In two other cases with nephrosis the serum cholesterol level was within the normal range. In the latter, the associated histologic renal lesions were less severe than those observed in the former group.

The blood urea nitrogen values were found to be inadequate reflections of the degree of renal damage as determined by renal histologic study unless the renal injury was severe. In five of the 13 patients with kidney injury of moderate degree the levels of the blood urea nitrogen were within the normal range. In all three members of the group who had severe renal involvement, however, the blood urea nitrogen was moderately to markedly elevated. Both the urine concentration test and the two-hour phenolsulphonphthalein excretion studies correlated poorly with the renal histologic changes; the 15-minute phenolsulphonphthalein excretion values correlated more satisfactorily with the pathologic findings.

The over-all degree of renal histologic damage was an accurate reflection of the ultimate prognosis as to the duration of life (Table 9). Two patients with minimal renal involvement are still alive from one to three years after the renal biopsy. Neither one has developed clinical evidence of renal injury. Five of the nine patients with moderate renal damage have died, but only three died from progressive renal failure. The remaining four members of this group are still alive from one to two years after the kidney biopsy study and only one has azotemia. Of the seven patients with advanced renal injury, three have succumbed to progressive renal impairment and four have moderate to marked nitrogen retention.

Attempts at Prevention of Renal Injury: Therapeutic attempts to prevent the development of renal injury, or to ameliorate it when present, were in-

stituted in 23 patients, of whom 10 had renal impairment. The patients without renal impairment received 200,000 units of penicillin orally once or twice a day for from one to five years. One patient received both penicillin and gamma globulin (10 c.c. intramuscularly each month) for two years. Six members of this group developed febrile exacerbations despite treatment, and two patients developed progressive renal involvement one year after the institution of penicillin therapy.

Of the 10 patients with renal damage, four received 200,000 units of oral penicillin daily for from one to six years; three were given 200,000 units of penicillin twice daily for one year; two were given gamma globulin, 10 c.c. intramuscularly, at monthly intervals for from one to three years; one patient received both gamma globulin and penicillin for eight months. The latter patient died of pneumonia 10 months after the initial hospital admission. The other nine patients are still alive although all have azotemia.

TABLE 10

Comparative Effectiveness of the Adrenal Steroids as Anti-inflammatory Agents in Man[13]

Hormonal Agent	Anti-inflammatory Activity	Average Initial Daily Oral Dose (mg.)	Average Daily Oral Maintenance Dose (mg.)
Cortisone	1	200–300	50–100
Cortisol	1–1.25	200–300	50–100
Prednisone	3–5	40–60	10–25
Prednisolone	3–5	40–60	10–25
6-methylprednisolone	3–5	32–48	8–24
3-methylcortisol	4–5	30–50	5–20
Desoxycorticosterone acetate	0	—	—
Aldosterone	0–?	—	—
9α-fluorocortisol	10–15	8–12	4–6
9α-fluoro-16-hydroxyprednisolone	3–5	32–48	8–24

Management of Disseminated Lupus Erythematosus: The treatment of systemic lupus erythematosus consisted of the use of corticotropin or the glucogenic steroids, or of their synthetic analogs.[2] Rigid restriction of the daily salt intake was necessary when the former two groups of hormones were employed. Salt restriction was not necessary when the synthetic analogs were administered (Table 10). When prolonged steroid therapy was contemplated the patient was also given daily supplemental potassium. Two to three grams of potassium chloride a day was usually adequate to prevent the development of hypokalemia. The synthetic analogs such as prednisone, prednisolone, and 6-methylprednisolone, tended less to induce a potassium diuresis than did the parent steroidal fractions.

The acute manifestations of the disease were promptly controlled when an adequate amount of hormone was administered. Table 10 lists the usual initial and maintenance doses of the various steroids with which we have had experience. Of particular importance is the immediate treatment of

intercurrent infections, particularly those of the upper respiratory tract, with the liberal use of antibiotics, since these infections may precipitate an acute exacerbation of the disease. When azotemia was present the protein intake was limited, usually to 40 gm. a day. Daily sodium restriction was instituted in patients with the nephrotic syndrome or chronic renal failure. The former frequently showed a gratifying response to salt and fluid restriction and hormone therapy, but unfortunately with the doses of the corticosteroids used this response was only temporary, the underlying renal damage progressing inexorably. Frequent electrolyte determinations were made to anticipate and to treat electrolyte imbalances. Anemia associated with azotemia responded poorly to therapy and occasionally necessitated transfusions with packed red cells. Because blood transfusion reactions are not uncommon in patients with systemic lupus erythematosus, this procedure should be used with caution.[3, 4]

Prognosis

Renal involvement in systemic lupus erythematosus is the least responsive of all the clinical manifestations of the disease, either to the adrenal glucogenic steroids or to corticotropin. Of 90 patients in our group 56 had renal involvement, 26 of whom have died. Of the latter, 22 lived for less than three years before succumbing to uremia (Table 11). The remaining four patients died of other causes, although all were azotemic at the time of death. Among the patients with impairment of renal function who are still alive, 13 have had the disease for from one to three years and 12 for from four to seven years. The latter group had less marked renal damage. Despite the administration of steroid therapy sufficient to control the other manifestations of systemic lupus erythematosus, no significant improvement in renal function was observed.. None of the patients without renal damage have succumbed to the illness. The three patients who developed renal disease after the first hospital admission did so despite adequate corticosteroid therapy.

Table 11

Survival Period of Patients with Renal Involvement*

Years	Died	Still Living
Less than 3	22	13
4–7	4	12
Over 7	0	0

* Of 26 patients without renal involvement in whom the follow-up has been adequate, none have died up to this writing. The period of observation thus far varies from six months to 10 years.

Discussion

The present study has served to emphasize the grave prognostic implications of involvement of the kidneys in systemic lupus erythematosus.[5–8] Evidence of persistent and significant impairment of renal function was

almost invariably encountered in those individuals who succumbed to the disease. The younger the individual, the greater was the frequency and severity of renal involvement.

The patients who had kidney damage generally manifested it early in the course of the illness. Only three of 58 patients with renal injury developed this complication subsequent to the first hospital admission, usually within one year. This indicates the importance of the initial laboratory studies in evaluating the prognosis in each instance. In a small number of patients with normal renal function, histologic evidence of nephritis was found. As shown by Muehrcke et al.,[8] such cases may subsequently develop clinical renal disease. In general, however, in the absence of clinical evidence of renal impairment within one year after the diagnosis is established, particularly if this is associated with a normal renal biopsy, the subsequent development of renal injury becomes unlikely.

Hypertension, when present, was almost invariably found in association with renal damage, although over 50% of this group failed to manifest this complication. Edema, particularly in association with hypertension, generally indicated a poor prognosis as to the duration of life.

The seriousness of the nephrotic syndrome is clearly evident in our studies. The mean duration of survival following the onset of nephrosis was eight months. These results are in agreement with the reports of others.[8-10] The normocholesterolemic variant, however, offered a somewhat better outlook in our series than did the findings of Muehrcke and his group.[8]

The anemia encountered in our patients was usually of the normochromic, normocytic type and unresponsive to iron therapy. A hemolytic component, however, may also be present. An additional cause for the anemia is the more specific bone marrow depression associated with azotemia. Acquired hemolytic anemia was present in four members of our group. In these instances a globulin "coating" of the patient's red cells was demonstrated by means of the direct anti-globulin technic. Treatment with corticotropin or the glucogenic steroids was effective in the control of the hemolysis.

The blood serum gamma globulin is characteristically elevated in systemic lupus erythematosus.[11] In several of our patients, however, normal or low gamma globulin levels were found and were usually associated with severe renal involvement. The alpha$_2$ globulin was frequently abnormally elevated and seemed to bear little relationship to the presence or absence of renal damage. In seven cases without renal damage, during an acute relapse of the illness when the temperature was considerably elevated, albuminuria, urinary cellular elements, and an elevation of the blood urea nitrogen were present. With the subsidence of the acute exacerbation the abnormal urinary constituents disappeared and the blood urea nitrogen value returned to normal levels. None of these patients subsequently developed renal impairment.

In the absence of hematoxylin bodies, the kidney of patients with sys-

temic lupus erythematosus may be indistinguishable from that seen in post-streptococcal glomerulonephritis.[8, 10, 12] A study of throat cultures and anti-streptolysin O titers in our group, however, failed to demonstrate more than a coincidental relationship between beta-hemolytic streptococcus infection and renal involvement. Neither penicillin nor gamma globulin appeared to prevent the development of renal injury or to ameliorate it when present. It is of interest, however, that nine of 10 patients with renal involvement treated with penicillin are still alive from one to five years later, although all have azotemia. This would suggest that antibiotic therapy may have prolonged the life of these patients, perhaps secondary to the prevention of intercurrent infections.

Renal involvement in systemic lupus erythematosus is the least responsive of all the clinical manifestations of the disease. Our study demonstrated that amounts of corticotropin or glucogenic steroids sufficient to suppress the clinical manifestations of systemic lupus erythematosus did not prevent or ameliorate renal damage. Muehrcke et al.[8] also noted no regression of structural damage to the kidney as determined by serial renal biopsy studies during treatment with corticosteroids. Recent reports suggest, however, that intensive and prolonged steroid therapy may produce a clinical and morphologic improvement in the renal status.[14, 15]

It is of some interest to observe that three women in our group had uneventful pregnancies and delivered normal babies while on steroid therapy. None of the three had renal involvement.

Summary

1. Renal manifestations were studied in 90 patients with systemic lupus erythematosus who were seen at the Mount Sinai Hospital from 1949 to 1959. The series included 56 with renal disease.

2. The study served to emphasize the grave prognostic implications of involvement of the kidneys in systemic lupus erythematosus. Evidence of persistent and significant impairment of renal function was almost invariably encountered in those individuals who succumbed to the disease.

3. The younger the individual, the greater was the frequency and severity of the renal involvement.

4. The patients who had kidney damage generally manifested it early in the course of the illness. The longer the disease continued without the development of this complication, the less likely was it to occur.

5. Hypertension, when present, was almost always found in association with renal damage, although over 50% of this group failed to manifest this complication.

6. The nephrotic syndrome was a serious complication. The mean duration of survival following the onset of nephrosis was eight months. The normocholesterolemic variant offered a somewhat better outlook.

7. The 15-minute excretion of phenolsulphonphthalein and the creatinine

clearance tests yielded the most useful information in terms of appraisal of renal status.

8. The anemia encountered was usually of the normochromic, normocytic type and unresponsive to iron therapy. An acquired hemolytic anemia was not infrequently encountered.

9. Elevation of the blood serum gamma globulin was the most frequent electrophoretic abnormality. When the gamma globulin levels were normal or low, there was usually severe renal involvement present.

10. A study of throat cultures and antistreptolysin O titers in our group failed to demonstrate more than a coincidental relationship between the beta-hemolytic streptococcus infection and the renal involvement.

11. The degree of renal histologic damage correlated well with the severity of the clinical manifestations and the ultimate prognosis. The 15-minute phenolsulphonphthalein excretion value correlated most satisfactorily with the renal pathologic findings.

12. Renal involvement in systemic lupus erythematosus is the least responsive of all the clinical manifestations of the disease. Our study demonstrated that amounts of corticotropin or glucogenic steroids sufficient to suppress the other manifestations of systemic lupus erythematosus had no effect either on the prevention or the amelioration of renal damage.

Acknowledgment

We wish to express our thanks to Dr. Jacob Churg for the histologic studies of the kidneys. He will subsequently publish a more detailed account of these observations.

Summario in Interlingua

1. Esseva studiate le manifestationes renal in 90 patientes con systemic lupus erythematose, vidite al Hospital Mount Sinai inter 1949 e 1959. Le serie includeva 56 casos con morbo renal.

2. Le studio servi a sublinear le grave pregnantia prognostic de affectiones renal in le presentia de systemic lupus erythematose. Evidentia de un grado significative de persistente dysfunction renal esseva incontrate quasi invariabilemente in le subjectos qui cadeva victima al morbo.

3. Quanto plus juvene le subjecto, tanto plus grande le frequentia e le severitate del affection renal.

4. Le patientes in qui le renes esseva lesionate manifestava iste facto generalmente a un periodo precoce del curso de lor morbo. Quanto plus longe le morbo continuava sin le disveloppamento del mentionate complication, tanto minus probabile esseva su occurrentia.

5. Hypertension, si presente, esseva quasi semper associate con dysfunction renal. Tamen, in le presente gruppo plus que 50% del casos non manifestava iste complication.

6. Le syndrome nephrotic esseva un serie complication. Le duration medie del superviventia post le declaration de nephrosis esseva octo menses. Le variante normocholesterolemic del syndrome nephrotic habeva un prospecto alique minus grave.

7. Le test del excretion de phenolsulfonphthaleina in 15 minutas e le test del clearance de creatinina produceva le plus utile information pro le evalutation del stato renal.

8. Le anemia incontrate esseva usualmente del typo normochromic, normocytic, non respondente a therapia a ferro. Acquirite anemia hemolytic esseva incontrate non infrequentemente.

9. Elevation del globulina gamma del sero del sanguine esseva le plus frequente anormalitate electrophoretic. Quando le nivellos de globulina gamma esseva normal o basse, grados sever de implication renal esseva usualmente presente.

10. Un studio de culturas de gurgite e le titros de antistreptolysina O in nostre gruppo non demonstrava plus que un relation coincidental inter infectiones per streptococco hemolytic beta e affection renal.

11. Le grado del vitiation histologic del renes esseva positivemente correlationate con le severitate del manifestationes clinic e del prognose final. Le test del excretion de phenolsulfonphthaleina in 15 minutas esseva correlationate le plus satisfacentemente con le constatationes de pathologia renal.

12. Le affection renal occurrente in systemic lupus erythematose es le manifestation clinic le minus responsive inter omne le manifestationes clinic de iste morbo. Nostre studio demonstra que corticotropina o steroides glucogenic in quantitates sufficiente a supprimer le altere manifestationes de systemic lupus erythematose habeva nulle effecto in prevenir o meliorar le implication renal.

BIBLIOGRAPHY

1. Davis, M. W., Gutridge, G. H.: Disseminated lupus erythematosus in identical twin sisters, associated with diabetes mellitus in one case. J. Missouri State Med. Ass. **48**: 446, 1951.
2. Soffer, L. J.: The therapy of systemic lupus erythematosus. J. Mt. Sinai Hosp. **26**: 297, 1959.
3. Race, R. R., Sanger, R.: Blood groups in man. 2d ed., pp. 358–359, Charles C Thomas, Springfield, Illinois, 1954.
4. Kuhns, W. J., Bauerlein, T. C.: Exchange transfusions in hemolytic anemia complicating disseminated lupus erythematosus. Arch. Intern. Med. **92**: 284, 1953.
5. McCombs, R. P., Patterson, J. F.: Factors influencing the course and prognosis of systemic lupus erythematosus. New Engl. J. Med. **260**: 1195, 1959.
6. Soffer, L. J., Bader, R.: Corticotropin and cortisone in acute disseminated lupus erythematosus: results of long-term use. J. A. M. A. **149**: 1002, 1952
7. Soffer, L. J., Ludermann, H. H., Brill, G.: Effect of corticotropin and adrenal steroids on the management of acute disseminated lupus erythematosus. Ann. N. Y. Acad. Sci. **61**: 418, 1955.
8. Muehrcke, R. C., Kark, R. M., Pirani, C. L., Pollak, V. E.: Lupus nephritis: a clinical and pathologic study based on renal biopsies. Medicine **36**: 1, 1957.
9. Dougherty, G. W., Bagenstross, A. H.: Syndrome characterized by glomerulonephritis and arthritis, Libman-Sachs disease with predominantly renal involvement. Arch. Intern. Med. **85**: 900, 1950.
10. Berman, L. B., Schreiner, G. E.: Clinical and pathologic spectrum of the nephrotic syndrome. Amer. J. Med. **24**: 249, 1958.
11. Jessar, R. A., Lamont-Hovers, R. W., Ragan, C.: Natural history of lupus erythematosus disseminatus. Ann. Intern. Med. **38**: 717, 1953.
12. Klemperer, P. Gueft, B., Lee, S. L., Leuchtenberger, C., Pollister, A. W.: Cytochemical changes of acute lupus erythematosus. Arch. Path. **49**: 503, 1950.
13. Soffer, L. J., Orr, R. H.: Editorial statement *in* Symposium: Newer hydrocortisone analogues. Metabolism **7**: part 2, 383, 1958.
14. Pollack, V. E., Pirani, C. L., Kark, R. M., Muehrcke, R. C.: Effect of large doses of prednisone on renal lesions of lupus glomerulonephritis. Clin. Res. **7**: 285, 1959.
15. Holman, H.: Systemic lupus erythematosus. J. Pediat. **56**: 109, 1960.

OCCUPATION, TRAUMA, AND CARDIOVASCULAR DISEASE *

By JULIEN H. ISAACS, M.D., F.A.C.P., *Beverly Hills, California*

HEART disease, known or unsuspected, may be aggravated by the effort, stress, or strain associated with occupational duties and the conditions under which these duties are performed. These subjects have been discussed and evaluated by medical and legal committees throughout the world. Medical and legal authorities alike have a large area of disagreement regarding the extent of damage and the aggravation or acceleration of heart disease that can result from occupational exertion and stress.

DEFINITIONS

Discussion of these problems necessitates definition of the terms "work," "effort," and "stress and strain." Occupational duties require work, effort, or exertion—that is, the expenditure of energy or power, either physical or mental (emotional). Work, then, suggests "toiling to achieve a desired goal." The term "stress and strain," however, suggests "stretching beyond the limits of normal." "Work" implies a normal physiologic process or activity; excessive effort or "stress and strain" suggest there is an abnormal response to this effort, an "injury."

EXCESSIVE EFFORT AND STRAIN

A recent report [1] queried 398 internists and cardiologists for their opinions on certain medical aspects of the effects of exertion and of stress and strain on the heart. An analysis of the answers should provide much insight into the physiologic effects of work and stress on the heart. Equivocal replies have been disregarded in figuring the percentages.

Can excessive effort or strain damage a normal heart? Ninety-four per cent of the physicians responded No; 1.5% responded Yes. The overwhelming majority of physicians believed that excessive effort and strain cannot damage a normal heart. The absence of pain of angina pectoris in association with extreme physical effort is significant. No athlete has been observed in cardiac distress during or following extreme competitive physical activity, such as a football game or an Olympic event. This opinion should hold for the majority of situations encountered.

Can a situation be defined wherein the minority opinion would be correct? Yater [2] has reviewed certain aspects of coronary heart disease in the Armed Forces in his report of 950 heart attacks (myocardial infarction)

* Received for publication March 22, 1960.

From the Department of Cardiology, University of Southern California School of Medicine.

Requests for reprints should be addressed to Julien H. Isaacs, M.D., 9735 Wilshire Boulevard, Beverly Hills, California.

studied at autopsy. Two per cent of these soldiers from the age group 18 to 29 years had myocardial infarction without coronary thrombosis or atherosclerotic changes in the coronary arteries. In the age group 50 and over, 4% of the soldiers with myocardial infarction were without evidence of coronary artery disease or coronary thrombosis. Cardiac damage (myocardial infarction) can develop without evidence of pre-existing heart disease, coronary artery disease or coronary thrombosis.

The degree of exertion preceding the onset of these attacks of myocardial infarction without pre-existing coronary artery disease was also reported. Twenty per cent of the soldiers in the younger age group experienced their heart attack while at rest or in bed, 32% with more strenuous activity, such as running or drill work, and the remainder during or following mild to moderate activity, such as regular, quiet walking. In the older age group, these figures were, respectively, 33%, 15% and 52%. No attempt was or could be made by Yater to study the emotional strain and tension associated with these attacks.

The circumstances in the above study establish one rule of thumb: each case must be analyzed in detail on its own merits.

Cardiac Disability and Pre-existing Coronary Artery Disease

Must coronary artery atherosclerosis precede the development of coronary occlusion and myocardial infarction? Ninety-four per cent of the physicians answered Yes, 6% answered No. Prolonged strain or effort can induce cardiac damage (myocardial infarction); prolonged strain has also induced coronary thrombosis. The incidence of this coronary thrombosis is rare, however, in the absence of pre-existing coronary artery atherosclerotic disease.

Sudden death without coronary thrombosis or myocardial infarction has been reported under conditions of effort and strain. Such sudden death is not uncommon with pre-existing coronary artery disease; it has occurred, but is quite rare in the absence of coronary artery disease. Sudden death without thrombosis or infarction is known as "mechanism" or "physiologic" death. It results from shock and circulatory collapse due to sudden cardiac standstill or very rapid or irregular heart rates; in these situations, the heart is incapable of pumping blood to the tissues of the body, and particularly to the muscle of the heart itself. Prolonged effort and strain of sufficient intensity can cause cardiac damage, severe cardiac dysfunction, or death, whether pre-existing coronary artery disease is present or not.

Relationship of a Second Myocardial Infarction to the First, and to Coronary Artery Disease

Is a second myocardial infarction causally related to the first, or to the underlying pathologic process or disease of the coronary arteries? Eighty-

three per cent of the physicians agreed that pre-existing coronary artery disease was the fundamental cause; 13% disagreed. There is little doubt that the basic disease process, atherosclerosis, involving the coronary arteries, inherently is responsible for both attacks.

Is there a possible situation wherein the minority opinion may be established? By definition, the initial attack of coronary thrombosis destroys a certain portion of cardiac muscle and thereby reduces the cardiac reserve. It follows, therefore, that a second coronary thrombosis may be induced by strain, stress, or exertion of lesser degree than that which produced the first attack. When considered in this manner, the second heart attack appears to have been in part accelerated by the first. If the first episode of coronary thrombosis has been determined to be an industrial responsibility, then, by similar reasoning, industry must bear a portion of the responsibility for the second attack.

Absolute medical criteria for placing this responsibility on industry are lacking, however. Medical authorities have established that coronary thrombosis is a complication of the basic disease process in the coronary

TABLE 1

The effect of excessive effort or strain, emotional and physical, on the heart [38]

1. Sudden death due to coronary artery disease, known or undetected.
2. Coronary thrombosis and/or myocardial infarction.
3. Acute coronary insufficiency.
4. Acute pulmonary edema or congestive heart failure.
5. Serious cardiac arrhythmia.
6. Rupture of heart muscle or valve.

Note: To establish a causal relationship between excessive effort or strain and a subsequent cardiac disease or dysfunction: (1) it is necessary for the symptoms to develop during the course of, or immediately following, the alleged stress or exertion, and (2) this stress or effort must be unusual or excessive for the particular individual concerned. Conversely, exertion and stress usual for the individual should not be considered to be a causative factor.

arteries—that is, atherosclerosis. Medically speaking, responsibility for this coronary artery and coronary heart disease should not and cannot be placed on industry. However, decisional and legislative laws have redefined these basic medical concepts by introducing the factors of aggravation, acceleration, and compensation. These factors have produced much inequity for both employer and employee; the effects of this compensation have not yet reached maximal proportions.

Moderately Heavy and Ordinary Daily Work: Can moderately heavy work without unusual exertion or strain produce cardiac injury? Is such injury related to employment? Eighty-nine per cent of the physicians answered No; 7% answered Yes. Consider a situation wherein an industrial worker has performed rather strenuous physical work for many years. Suddenly he suffers a heart attack during performance of similar heavy work. Can there be a causal *medical* relationship between this heavy work and the onset of the heart attack? Physicians arguing against this causal relationship state that there has been no unusual effort or strain in this

instance (Table 1). Physicians believing there may have been a cause-and-effect relationship have recommended that (1) the circumstances and emotional pressures preceding the onset of this heart attack be determined, and (2) an attempt be made to ascertain whether the cardiac status at the time of the attack was in fact identical with that on previous working days.

These considerations can be clarified only by detailed analysis of the circumstances and actions preceding, during, and following the heart attack. Perhaps this strenuous work was performed under some handicap, such as emotional pressure or tension; or perhaps the coronary artery disease, atherosclerosis, with its narrowed coronary arteries, had progressed to a degree where exertion similar to that on the previous day had become excessive for this heart.

Mental and emotional stress may compromise cardiac reserve and function to aggravate cardiac disability, even though the individual is performing the same physical effort as on prior working days. A causal relationship between regular occupational effort and an ensuing heart attack can be established only by determining the exact details of work and effort preceding and following the attack, and by considering the comments of the worker, his emotional state prior to the attack, and all other extraneous factors that may have been present.

The problem of ordinary, everyday effort or work and its effect on the heart is extremely difficult for many physicians to comprehend. It is impossible to determine when ordinary effort becomes a strain. Medical criteria for these borderline regions can be used at best only as a guide. Each instance is different; what is strain for one individual is light work for another. Each occurrence can be categorized only by a detailed analysis of the situation preceding and following the traumatic event.

Work Classification Studies: Competent medical authorities [3-6] have agreed that 80 to 85% of individuals who have experienced an attack of coronary thrombosis can return to work safely if the following conditions obtain:

1. There is adequate medical care.
2. The patient has been carefully evaluated for individual work capacity by work classification methods.
3. The patient has been placed selectively in a job well within the limits of his physical and mental capabilities.
4. The patient has received the assurances necessary to allay the anxieties that so frequently accompany cardiac disease.

Each instance of coronary thrombosis must be individually judged in regard to return to work. The majority of postcoronary individuals returning to work continue in their former occupations. The most important factor in this return to work is the status of the heart (cardiac reserve). The second most important, and the greatest deterrent to rehabilitation, is the emotional state of the patient. Emotional problems are present in

almost 50% of all coronary thrombosis patients. In this group, disability and distress are based on fear, anxiety, and tension states in an *already susceptible individual.* Fatigue outweighs all other symptoms, and is far greater than would be anticipated for the simple exertional expenditure of energy. Psychologic factors predominate in the rehabilitation of postcoronary individuals.

Work classification studies by Hellerstein and others [7, 8] have uncovered many individuals with cardiovascular disease working at standard occupations in industry; 35 to 60% of these individuals had had at least one myocardial infarction. These postcoronary individuals were not restricted to light work; in many cases, their jobs necessitated moderate to extreme effort for short periods. About 35% of the cardiacs discovered in these occupational studies were determined to have had a silent myocardial infarction; many of them were also performing heavy physical work without symptoms.

It is not surprising to cardiologists that so large a group of postcoronary individuals are working in heavy industrial jobs. Hellerstein et al.[8] have determined that the average energy expenditure for 90% of all industrial jobs is approximately three calories per minute or less. This is no greater expenditure of energy per minute than that utilized in washing, dressing, and shaving. Maximal energies utilized in industry for short periods during the work day were seldom raised above six calories per minute; this is similar in energy requirements to a moderately paced walk of a few blocks. Under adequate conditions, the cardiac individual can perform the same work as a noncardiac individual, and with as much efficiency and without harm to himself or to others. Certain occupations obviously must be restricted to noncardiac individuals, to prevent possible injury to other persons (e.g., airline pilots, drivers of public vehicles).

These factors of cardiac reserve and emotional tension can be readily approximated. Physicians have been classifying postcoronary individuals as to their physical and emotional capacities for some years. Objective studies can be made in the average physician's office. Occasional subjects require special data; for these, work classification study units have been established in many large medical centers in association with the local heart association.

Disability Status After Recovery from Myocardial Infarction: Does a permanent partial disability result after recovery from myocardial infarction and return to work totally without symptoms? Forty-six per cent of the physicians believed there was such a disability, and 48% believed no disability was present. Myocardial infarction is defined as destruction of cardiac muscle fibers with replacement by scar tissue. Infarction, then, must reduce the total amount of active cardiac muscle, and hence lessen the cardiac reserve. Small or clinically insignificant loss of myocardial reserve, for all practical purposes, should not produce any evident disability, partial or

otherwise. Detecting and establishing such disability on an objective basis would be impossible. Larger segments of damaged muscle, even with complete absence of symptoms, may reduce the cardiac reserve to a point just above the safety margin necesary to keep the subject free of symptoms. A sudden stress or strain excessive for this individual may place him over the limit of his tolerance, producing severe symptomatology and cardiac damage. Permanent partial disability in these subjects is a probability; this probability can be determined only on a quantitative basis.

Effect of Emotional Stress on the Heart

Emotion plays an extremely important part in the action of the cardiovascular system. A large majority of medical authorities believe emotional factors play a significant role in bringing on a heart attack, and that these factors are more important than the factor of physical exertion.

John Hunter, a famous physician, suffering from angina pectoris, stated: "My life is in the hands of any scoundrel choosing to make me angry." Certain angina patients are capable of moderately active walking and vigorous washing in a shower without distress, but suffer cardiac pains when attempting to aid their wives in washing a few dishes. Forty-one persons listening to the first nationwide broadcast of a major sporting event, the Dempsey-Tunney boxing match in the early 1920s, were reported to have died during the dramatic "long count." Russek,[9] Wolff,[10] and others [11, 12] have reported that 90% of postcoronary individuals studied by them had had prolonged emotional stress preceding the attack of coronary thrombosis.

Wolff [10] has measured heart rate, blood pressure, oxygen uptake, and various other cardiovascular variables in normal subjects before, during, and after standardized exercise test. All subjects developed a rise in these physiologic values during and immediately following this exercise. In the normal relaxed individual, these measured cardiovascular characteristics returned to their normal resting state within a few minutes after the exercise test was completed. If the same normal individual was made to perform these exercise tests under unfavorable conditions—for example, where he would obviously fail because he had an unsavory task or a difficult mental calculation to perform simultaneously with the exercise—the cardiovascular responses remained elevated more than 48 hours after the exercise was discontinued. These same abnormal responses developed if individuals who were severely fatigued or were having domestic difficulties were made to perform these same exercise tests. Depressed individuals responded to these exercise tests with a sudden drop in the measured cardiovascular responses, including a drop in blood pressure and heart rate; often they experienced typical cardiac chest pain and developed moderately severe electrocardiographic changes of acute coronary insufficiency.

Wolff [10] also studied asymptomatic subjects known to have minimal coronary artery disease (atherosclerosis) but no clinical evidence of heart disease. Continuous electrocardiographic tracings were made during psychiatric interviews. When these subjects were confronted with their significant emotion-laden life situations, the electrocardiogram recorded sudden abnormal ectopic beats, paroxysmal tachycardias, and often the typical changes of acute coronary ischemia; many subjects experienced anginal pain. When they were visibly relaxed by soothing talk, the abnormal findings spontaneously disappeared. In certain subjects these abnormal rhythms could be "turned on and off" by the therapist with appropriate symbolization and aids to relaxation.

Work-energy utilization studies by Hellerstein [8] on surgeons before, during, and after they performed a surgical procedure established that the calories per minute expended were occasionally equal to the calories utilized for active treadmill exercise. In addition, the myocardial oxygen consumption during stressful surgery was found to be equal to that consumed in moderate to severe exercise. Surgeons reacting in this manner during surgery were obviously under tension and anxiety; their cardiac work load was considerably greater than the physical effort required.

Wolff [10] has summarized these problems well. He stated that man is so constituted that he is vulnerable by his reaction not only to the actual existence of danger, but also to threats of symbols of assaults experienced in his past. Assault symbols call forth reactions very little different from the assault itself. The "heart" and "cardiac disease" are great danger symbols to man. The man with heart disease doubts his ability to "live the life of a man," that is, to hold his job, have security, and provide for his family. Each person has his own symbols; what is a significant, emotion-laden symbol for one individual has no meaning for another, nor is there a standard emotional assault. These physiologic cardiovascular responses to emotionally significant symbols are in reality a mobilization for defense. In a chronic state of stress and strain, the individual may be suggested to be in a state of perpetual preparation for action.

Emotion and Heart Disease: Emotional stress can endanger pre-existing heart disease—this is unchallengeable. Can emotional stress of sufficient duration and intensity induce or cause heart disease? Many medical authorities are convinced of this causal relationship. Sprague [13] and Russek,[9] separately, have postulated this causal relationship as follows: Emotional tension produces compulsive eating, drinking, and smoking in many individuals as compensation for anxiety; it also produces fatigue and loss of vigor well beyond simple exertional demands. Emotional tension, through this indirect mechanism, contributes to the individual's failure to achieve daily physical exertion. Emotional tension, together with the social and economic pressures of modern society, has forced these individuals into commitments far beyond their capacity, thus interfering with their leisure time and relaxation.

The aforementioned examples illustrate the profound physiologic effects of emotion on the heart and cardiovascular system. Heavy work and physical exertion may endanger the heart, but worry, tension, pressure and emotional strain in association with such work may cause much greater damage. Therefore, if it is necessary to work hard or for long hours under pressure, under prolonged strain or tension, or with much aggravation, the wise person will *"have and enjoy"* a satisfactory period of rest and relaxation afterwards. The heart will repair itself if given the necessary rest periods.[9-13]

Legal and Medical Relationships

Determining a causal relationship between occupational stress and cardiac dysfunction or disease necessitates concise criteria. One classifica-

tion of these medical criteria has been offered (Table 1). Legal and medical authorities have differed markedly in their acceptance and interpretation of these criteria. A causal relationship between occupation and heart disease must therefore be based on the details and merits of each individual case; time relationship between a heart attack and the alleged trauma and the conditions under which the work was accomplished are all important.

Much improvement is needed both in medical criteria and in legal decisions regarding cause and effect. The basic goal of both the medical and the legal professions should be rehabilitation and return of the cardiac individual to a normal social and economic activity, that is, gainful employment. Enlightened industrial physicians in many modern corporations have established that this goal is well within the realm of possibility.

Direct Traumatic Injury to the Heart

Direct traumatic injury to the heart may be classified into nonpenetrating and penetrating chest injuries.

Nonpenetrating injuries may be caused by many mechanisms, including (1) a direct blow to the chest wall, with contusion or laceration of the epicardial (outer) surface of the heart; (2) indirect force producing an increased intravascular hydrostatic pressure within the heart, such as may occur with compression or crushing injury to the abdomen or extremities; (3) compression of the chest; (4) sudden decelerative, blast, and concussive forces; or (5) any combination of these.

Penetrating wounds of the heart result when foreign bodies pass through the body into the cardiac tissues. The route of approach may be (1) through the chest wall, from any position; (2) through the esophagus or bronchial tree; or (3) through vascular channels migrating into the heart.

Penetrating wounds may be very serious, but are not common in civilian existence. Nonpenetrating wounds involving the heart are more common; many instances pass unrecognized, the symptoms and findings having been blamed on direct chest cage injury, as fractured ribs and soft tissue (muscle and ligament) injuries. Nonpenetrating cardiac injury *must* be anticipated with any blow to the chest, however minimal this blow may appear to be. Case reports with autopsy [14] have been presented wherein individuals were hit on the chest, one by a stick, another by a pitched ball; both individuals died a few moments later.

One of the common causes of cardiac injury due to nonpenetrating wounds is the automobile accident during which the chest has been crushed suddenly against the steering wheel or dashboard following sudden deceleration.[15–17] The jack hammer [18] used in the digging up and paving of streets has caused cardiac contusion and myocardial infarction. Electric shock [19, 20] resulting in myocardial infarction has also been reported. The majority of nonpenetrating cardiac injuries do not leave permanent or serious disability. An optimistic approach to full recovery is justified unless there is definite evidence to the contrary. Minor traumatic cardiac injuries, with good and

full expectation of recovery, often result in neurotic disability in previously susceptible individuals. Great care must be taken to avoid this complication.

The greatest problem, by far, from nonpenetrating injuries to the heart occurs in individuals with pre-existing coronary artery disease or coronary heart disease. This problem exists whether the pre-existing heart disease is known or remains undetected. The factor of pre-existing heart disease cannot be evaluated accurately in every case; nevertheless, it is a fact well known and accepted by medical authorities that individuals with pre-existing heart disease are more susceptible to trauma than are individuals with normal cardiovascular apparatus.

Trauma and Pre-existing Heart Disease

Trauma to any portion of the body may and does produce more serious cardiac disability to those individuals with pre-existing coronary artery and heart disease than to individuals with normal cardiovascular apparatus. This cardiac disability develops earlier than would be anticipated from the natural course of the heart disease.

Much clinical and experimental evidence may be cited to substantiate these statements; a few illustrations should suffice. Cardiac disability following a traumatic experience has been noted to occur in older persons with greater frequency. It is presumed that older persons have a greater incidence of coronary artery and heart disease. This presumption is largely true; young adults and children can and do sustain more extensive traumatic injuries without significant cardiac disability.

Animal experiments designed to study sensitivity of the heart to external trauma illustrate the greater sensitivity for cardiac disability with pre-existing heart disease. Cats with cardiac disease produced by surgical changes in the aortic valves [21] were more sensitive to controlled injury (contusion) than was a similar control group of cats. Arrhythmias developed with greater frequency, and were more serious; myocardial hemorrhages were more extensive; and sudden death was more frequent. Similar observations were made by these same investigators [21] on rabbits made arteriosclerotic by special cholesterol feeding experiments. Hypersensitivity of the heart to injury [21] was also produced in dogs and rabbits poisoned with digitalis and thyroxin.

Another investigator [22] injected rabbits with horse serum and subsequently submitted them to controlled external contusion. These animals developed areas of atonic muscular contraction in the heart that were pale and anemic in gross appearance, not unlike areas of myocardial infarction; these areas did not contract during cardiac systole, but rather ballooned out, in a manner similar to that of areas of infarction. These effects were not observed in control rabbits subjected to the same contusional injury.

Aggravation of pre-existing cardiac disease by trauma cannot be doubted, but the degree to which trauma is responsible for disability is a most difficult medicolegal problem. The role of trauma in aggravating and accelerating disability due to previously existing heart disease often cannot be estab-

lished with certainty. No direct or complete answer to this problem is possible; each instance must be judged on its own merits.

Cardiac Disability Following Trauma External to the Heart and Thorax

Trauma remote from the heart and chest cage can produce cardiac injury.

A four-year-old boy run over by a truck was found to have a fractured pelvis but no evidence of injury to the chest wall; he died soon afterward. At autopsy there was found a rupture of the left ventricle, with marked bleeding into the pericardium.[23] A 44-year-old male, digging in the sand, was buried to the waist by a cave-in; unconsciousness and death followed rapidly. Autopsy revealed extensive damage to the heart and aorta with (1) lacerations through the interventricular septum, producing an opening between and into both ventricles; (2) torn papillary (valve) muscles; (3) laceration of the right auricle; and (4) separation of the aorta from its root at the heart.[24]

Even with total absence of visible external trauma, cardiac damage may result. Passengers in an airplane crash do not experience direct injury, for they are belted or anchored to the seat; rather, they are subjected to sudden decelerative forces. A pathologic study of individuals injured in such airplane accidents [25] has noted tears or rupture of the heart and aorta, especially involving the right auricular endocardium; these tears often extended through the wall to produce rupture and hemopericardium, or a laceration of the aorta.

Sigler [26] has stated: "Trauma of the heart may occur as a result of a blow to any part of the body provided it is of sufficient violence and its force is transmitted to the heart." Rupture of the heart, pericardial and epicardial changes, congestive heart failure, coronary thrombosis and myocardial infarction, as well as abnormal electrocardiographic changes without symptoms, have been noted to result from fractures of the skull, pelvis, or legs, or from other injuries peripheral to the heart.

Sprague [27] has outlined some of the factors and conditions in remote trauma responsible for cardiac disability (Table 2). He has also outlined his recommendations for analysis of a causal relationship between trauma and heart disease, as follows:

Table 2

The effect on the heart of trauma remote from the heart and chest cage [27]

A. In the absence of shock, there may be:

1. Subacute bacterial endocarditis following dental extraction.
2. Activation of acute rheumatic fever or rheumatic carditis by surgery or injury to any part of the body.
3. Auricular fibrillation and other abnormal cardiac arrhythmias resulting from severe effort, injury, or electric shock.
4. Ventricular arrhythmias resulting from inhalation of noxious gases or fumes.
5. Myocardial necrosis, angina pectoris, or congestive heart failure following inhalation of carbon monoxide in subjects with pre-existing coronary artery disease.
6. Rupture of normal heart valves and certain of their supporting structures, such as the chordae tendineae; this has been reported following cranking of an automobile engine.

B. In the presence of shock, relative coronary ischemia, or anoxia, myocardial infarction may result, with or without coronary thrombosis; this may follow:

1. Lowered coronary artery blood pressure or blood flow associated with:
   a. Sleep, shock, abnormally rapid heart rates, and hemorrhage.
   b. Drop in blood pressure following exertion.
   c. Dehydration.
   d. Valsalva maneuver accompanying exercise and effort.
2. Increased coronary artery blood pressure associated with pain, exertion, and emotional stress; these may result in:
   a. Rupture of atheromatous plaques in a coronary artery and eventual hemorrhage, thrombosis, and myocardial infarction.
   b. Rupture of an abnormal capillary vessel in the myocardium, with resulting hemorrhage and softening in adjacent cardiac muscle.
   c. Hemorrhage into the wall of a coronary artery, with eventual thrombosis and myocardial infarction.
3. Anoxia associated with:
   a. Coronary artery spasm after meals, and with hiatus hernia, duodenal ulcer, and gallbladder disease.
   b. Ischemia of effort in individuals with pre-existing heart disease or coronary artery disease.
   c. Carbon monoxide poisoning.
   d. Certain vitamin deficiencies.
   e. Certain drugs in excess: digitalis, thyroxin, and epinephrine.
4. Fatigue.

A detailed history must be obtained as soon as possible after the alleged trauma, including:

1. The physical and emotional state of the subject prior to the trauma.
2. The emotional pressures during the preceding few days.
3. The physical activities prior to the trauma.
4. The customary physical and emotional habits of the subject.
5. The circumstances and events immediately following the trauma.

An exact determination of the degree of injury is necessary, including:

1. The subsequent history of cardiovascular symptomatology.
2. The objective evidence for cardiovascular disease or dysfunction.
3. An assessment of the neurotic status of this individual and the effect of compensation and litigation.

The final status of this cardiac injury must be learned, whether there has been recovery, partial or total disability, or death. If death has resulted, a detailed autopsy must be made.

Work, Trauma, and Hypertension

Blood pressure normally is elevated during work, effort, and exertion.[28] During light exercise, blood pressure may remain at a normal level or elevate slightly. Vigorous exercise may increase the systolic blood pressure to levels of 180 or 200 mm. Hg. After exercise ceases, blood pressure returns to the normal level within a few minutes.

During sleep, blood pressure may drop 10 to 30 mm. Hg. Disturbing or exciting dreams may elevate the systolic blood pressure well above that encountered in normal walking (125 to 130 mm.), that is, to 180 or 200 mm. Hg.

These instances of blood pressure elevation do not imply hypertension or hypertensive vascular disease. Hypertension [29] implies an elevation of the basal blood pressure above an arbitrarily selected level, usually 140/90 mm. of Hg. Elevation of blood pressure due to physiologic vasoconstriction or transient increase in cardiac output due to emotion, cold, and other trivial causes is common, and modifies the significance of a casual high blood pressure reading. Hypertension or hypertensive vascular disease should indicate an increase above normal of the total peripheral arterial resistance. This peripheral resistance is measured by dividing the mean arterial blood pressure by the cardiac output. Elevation of blood pressure due to increased cardiac output per stroke of the heart or increased cardiac rate is not necessarily hypertensive disease.

Normal and hypertensive subjects develop an increase in blood pressure levels during and immediately following standard exercise tests. Normal subjects return to basal levels within a few minutes after the exercise is discontinued. Hypertensive subjects display a greater level of blood pressure rise, and this elevated blood pressure persists for longer periods after exercise has ceased. These data have been determined experimentally by many investigators.[30-32]

Similar elevated blood pressure responses were noted in normal and in hypertensive individuals subjected to psychic stress. Blood pressure under psychic stress was elevated to higher and more sustained levels in hypertensive than in normal individuals.

Hypertensive subjects have greater vascular reactivity and a slower return to their resting blood pressure levels. Marked individual variability is present, however, and the degree of response overlaps in both groups. Nevertheless, it is of statistical significance that hypertensive subjects under stress experience a greater and more sustained elevation of blood pressure than do normal subjects.[9, 33-36]

Hypertension Directly Caused by Trauma: Hypertensive vascular disease may occur in association with, or result from or follow as a secondary effect of dysfunction of a traumatized organ or organs. Hypertension may be an effect secondary to the pain and emotional stress associated with the trauma. This form of hypertension may be considered to be only an aggravation of pre-existing tendencies; it is transient, and usually will subside with adequate therapy directed to the essential factors.

Hypertension is also commonly found with many specific injuries, especially: (1) unilateral injury to renal arteries; (2) severe infection; (3) amputation of a major portion of an extremity; and (4) central nervous system injuries. The simultaneous presence of hypertension and a traumatic injury does not necessarily imply a causal relationship between the trauma and the hypertension. Each instance of traumatic injury where hyperten-

sion is found to be present must be studied on its own merit. The following are important characteristics to be determined in establishing a causal relationship between hypertension and trauma:[37]

1. Time relationships between the symptoms of traumatic dysfunction and the manifestations of hypertension.
2. Location of the trauma, organs or organ involved, degree of damage resulting, presence of infection, and degree of pain.
3. Occurrence in younger age groups (favors traumatic origin).
4. Exclusion of symptoms or manifestations of hypertension existing prior to the trauma, especially left ventricular hypertrophy and retinal vessel changes characteristic of hypertensive disease.
5. Exclusion of other familial traits of hypertension.

The last two characteristics suggest that the hypertension is not a direct result of trauma, but only an aggravation of a pre-existing hypertension or hypertensive tendency.

Summary

1. Occupational stress or trauma may and can aggravate or accelerate as well as directly and indirectly cause cardiovascular disease and dysfunction.

2. Individuals with pre-existing cardiovascular disease, particularly coronary artery and coronary heart disease, known or undetected, are more susceptible to and develop more extensive cardiac disability from trauma or occupational stress.

3. Establishing a causal relationship between cardiovascular disease or disorder and the alleged traumatic or occupational stress requires careful consideration of medical criteria and detailed analysis of circumstances and events preceding and following the alleged causative factor(s). Objective as well as subjective evidence should be available to establish the nature and extent of a resulting cardiovascular disorder.

4. Permanent status resulting from the trauma or occupational stress must be accurately determined, whether full recovery, partial or total disability, or death.

Summario in Interlingua

Il es possibile e il occurre que stress o trauma occupational augmenta le gravitate e accelera le curso de morbo e dysfunction cardiovascular. Il es etiam possibile e il etiam occurre que stress o trauma occupational es le causa de morbo e dysfunction cardiovascular. Establir un nexo causal inter morbo o dysfunction cardiovascular e un possibile stress de character traumatic o occupational require le meticulose consideration de criterios medical e le detaliate analyse del circumstantias e eventos precedente e sequente le incriminate factor o factores causal. Un objective demonstration debe esser effectuate in supporto de omne assertion con respecto al natura e al grado del resultante disordine cardiovascular. Le permanentia del stato re-

sultante ab le trauma o ab le stress occupational debe esser determinate accuratemente. Il debe esser determinate si le patiente se restabli completemente o si le resultato es un invaliditate partial o total o mesmo le morte del patiente. Quando il existe le possibilitate que le causa del morte del patiente es trauma o stress occupational, un precisissime necropsia debe esser interprendite.

Subjectos con pre-existente morbo cardiovascular, particularmente morbo de arteria coronari e morbo cardiac coronari (sin reguardo a si le condition es cognoscite o occulte) es plus susceptibile de disveloppar invaliditate cardiac in consequentia de trauma o stress occupational. In tal casos le resultante condition etiam tende a esser plus extense.

Es presentate tabulas pro illustrar un possibile methodologia pro le elaboration de criterios relative al mentionate relationes causal. Tal criterios non pote esser absolute; illos representa solmente un guida. Es discutite factores particular e le relation inter morbo e dysfunction cardiovascular e le incriminate factores causal.

Multe melioration methodologic es requirite in le campo del criterios medical e del jurisprudentia decisional con respecto al question de causa e effecto. Le ultime objectivo del profession legal si ben como del profession medical deberea esser le rehabilitation del subjecto cardio-pathologic a un vita de normal activitate social e economic.

BIBLIOGRAPHY

1. Ehrlich, H.: The cardiac problem, "Appendix A" in the Report to the Honorable Averell Harriman, Governor of the State of New York, by Moreland Commissioner Joseph M. Callahan, covering Costs, Operations and Procedures under the Workmen's Compensation Law of the State of New York. Compens. Med. **9**: 7, 1957.
2. Yater, W. M., Welsh, P. P., Stapleton, J. F., Clark, M. L.: Comparison of clinical and pathologic aspects of coronary artery disease in men of various age groups: a study of 950 autopsied cases from the Armed Forces Institute of Pathology. Ann. Intern. Med., **34**: 352, 1951.
3. Slipyan, A.: Effect of competitive industrial activity on severely disabled patients. J. A. M. A. **168**: 147, 1958.
4. Washington State Heart Association Booklet: Employment of the Cardiac, 1956 (out of print).
5. Goldwater, L. J., Bronstein, L. H., Kresky, B.: Returning cardiacs to work. American Heart Association, New York, 1952.
6. Aronson, S. F.: Effects of effort on the diseased heart; medicolegal implications. Northwest Med. **55**: 54, 1956.
7. Conference on Heart in Industry, New York City, reported in Medical Science **5**: 458 (Apr. 10) 1959.
8. Hellerstein, H.: The cardiac in industry, presented at the Los Angeles County Heart Association Symposium, Los Angeles, October, 1959.
9. Russek, H. I.: Role of heredity, diet and emotional stress in coronary heart disease. J. A. M. A. **171**: 503, 1959.
10. Wolff, H. G.: Life stress and cardiovascular disorders. Circulation **1**: 187, 1950.
11. Gertler, M. M., White, P. D.: Coronary heart disease in young adults, multidisciplinary study, Cambridge, Mass., published for The Commonwealth Fund by Harvard University Press, p. 65, 1954.
12. Wolf, S.: Cardiovascular reactions to symbolic stimuli. Circulation **18**: 287, 1958.
13. Sprague, H. B. (Editorial): Emotional stress and the etiology of coronary artery disease. Circulation **17**: 1, 1958.
14. Parmaley, L. F., Manion, W. C., Mattingly, T. W.: Non-penetrating traumatic injury of the heart. Circulation **18**: 371, 1958.

15. Hilmar, W.: Commotio cordis in expert testimony. München. med. Wchnschr. **99**: 1730, 1957.
16. Hale, H. W., Jr., Martin, J. W.: Myocardial contusion. Amer. J. Surg. **93**: 558, 1957.
17. Kahn, M. H., Kahn, S.: Cardiovascular lesions following injury to the chest. Ann. Intern. Med. **2**: 1013, 1929.
18. Borodkin, H. D., Massey, F. C.: Myocardial trauma produced by non-penetrating chest injury. Amer. Heart J. **53**: 795, 1957.
19. Hundt, H. J.: Electrocardiographic changes simulating cardiac infarction after electrical accident. Ztschr. f. Kreislaufforsch. **44**: 941, 1955.
20. Audier, M., Ruf, G.: Cardiovascular disorders caused by electrical accidents. Semaine d. hôp., Paris **32**: 666, 1956.
21. Külbs, F., Strauss, L. H.: Heart and trauma. Klin. Wchnschr. **11**: 1572, 1932.
22. Schlomka, G., cited by Mainzer, F.: Heart contusion and coronary disease. Cardiologia **16**: 287, 1950.
23. Saphir, O.: Rupture of the heart by indirect trauma in a four year old boy. Amer. J. Med. Sci. **173**: 353, 1927.
24. Kellert, E.: Traumatic rupture of the heart. J. Lab. Clin. Med. **2**: 726, 1917.
25. Hass, G. M.: Types of internal injuries of personnel involved in aircraft accidents. J. Aviation Med. **15**: 77, 1944.
26. Sigler, L. H.: Traumatic injury of the heart; incidence of its occurrence in forty-two cases of severe accidental bodily injury. Amer. Heart J. **30**: 460, 1945.
27. Sprague, H.: The effect of trauma and strain on the production and aggravation of heart disease. Bull. New York Acad. Med. **23**: 631, 1947.
28. Best, C. H., Taylor, N. B.: Physiological basis of medical practice, 5th Ed., The Williams and Wilkins Company, Baltimore, 1950.
29. Wood, P.: Diseases of the heart and circulation, J. B. Lippincott Co., Philadelphia. 1957.
30. Wolf, S., Wolff, H. G.: Experimental evidence for hypertension, *in* Hypertension: a symposium, edited by E. T. Bell, University of Minnesota Press, Minneapolis. 1951.
31. Fraser, R. S., Chapman, C. B.: Studies on the effect of exercise on cardiovascular function. II. The blood pressure and pulse rate. Circulation **9**: 193, 1954.
32. Stevenson, I. P., Duncan, C. H., Flynn, J. T., Wolf, S.: Hypertension as a reaction pattern to stress. Correlation of circulatory hemodynamics with changes in the attitude and emotional state, Amer J. Med. Sci. **224**: 286, 1952.
33. Harris, R., Sokolow, M., Carpenter, L. G., Kalis, B. L.: Consistency of response to psychologic stress in prehypertensives and in patients with essential hypertension. Circulation **12**: 719, 1955.
34. Pickering, G. W.: High blood pressure, Grune and Stratton, New York. 1955.
35. Kalis, B. L., Harris, R. E., Sokolow, M., Carpenter, L. G.: Response to psychologic stress in patients with essential hypertension. Amer. Heart J. **53**: 572, 1957.
36. Levy, R. L., White, P. D., Stroud, W. D., Hillman, C. C.: Transient hypertension; the relative prognostic importance of various systolic and diastolic levels. J. A. M. A. **128**: 1059, 1945.
37. Heinze, G.: Forms of hypertension caused by trauma. Med. Klin. **52**: 1331, 1957.
38. Guide for establishing causal relationships between trauma or strain and heart disease. Recommendations of the Committee on Workmen's Compensation of the Washington State Heart Association. Northwest Med. **55**: 55, 1956.

HEMODYNAMIC STUDIES IN ACUTE PULMONARY EDEMA *†

By JAMES K. FINLAYSON, M.B., M.R.C.P.,‡ MILTON N. LURIA, M.D., C. ALPHEUS STANFIELD, M.D., and PAUL N. YU, M.D., F.A.C.P.,
Rochester, New York

DATA on the hemodynamic changes which occur during acute pulmonary edema in man are still relatively scanty although a few workers have published their findings in this condition.[1-4] Recently in our laboratory we studied five patients who developed acute pulmonary edema during cardiac catheterization. In each patient the onset of pulmonary edema was evidenced by acute dyspnea, cough, mental distress, and the development of râles throughout the lung fields. In one patient frothy pink sputum was expectorated. We present our methods and our results below.

METHODS

The patients were studied in the supine position and all pressure measurements were referred to the level of the right atrium. Systemic arterial pressure was measured using an intra-arterial needle connected to a strain gauge manometer; right heart and pulmonary vascular pressures were measured by a cardiac catheter connected to a similar strain gauge manometer. These pressures were recorded on a Sanborn Polyviso Cardiette.

Cardiac output was measured by the Fick procedure or by the indicator dilution technic. Oxygen consumption was determined by measuring respiratory minute volume and oxygen content of expired air by Scholander microanalysis. The oxygen content and capacity of the blood were analyzed by the manometric method of Van Slyke and Neill.

In one patient, pulmonary diffusing capacity and pulmonary capillary blood volume were estimated by means of the single-breath carbon monoxide method, at multiple oxygen tensions.[5]

PATIENTS STUDIED

Of the five patients studied, two had pure mitral stenosis, one had mitral stenosis with systemic hypertension, one had mitral stenosis with mild aortic

* Received July 19, 1960.
Presented at the Forty-first Annual Meeting of The American College of Physicians, San Francisco, California, April 6, 1960.
From the Cardiopulmonary Laboratory, Department of Medicine, University of Rochester School of Medicine and Dentistry, and Medical Clinics of Strong Memorial and Rochester Municipal Hospitals, Rochester, New York.
† This study was supported in part by research grants-in-aid from the National Heart Institute (H-3966), the American Heart Association, the New York Assembly, and the Livingston, Cayuga, and Monroe County Heart Chapters.
‡ This work was done during the tenure of an Exchange Fellowship from the Board of Management for Aberdeen General Hospitals, Aberdeen, Scotland.
Requests for reprints should be addressed to Paul N. Yu, M.D., Strong Memorial Hospital, 260 Crittenden Boulevard, Rochester 20, New York.

TABLE 1

Hemodynamic Data on Five Patients With Acute Pulmonary Edema

Patient	Age and Sex	Diagnosis	BSA	Period	Pressures (mm. Hg)				C.I.	AV_{O_2} Diff.	H.R.	D.F.P.
					PA_M	PC_M	R.V.	Systemic Artery Mean				
I. B.	48 F	M.S. Hyper-tension	1.64	I	84	35	—	125	—	—	100	35
				II	113	—	—	140	2.90	87.8	130	35
				III	58	—	82/8	90	—	55.5	100	39
F. C.	35 F	M.S.	1.52	I	47	27	—	—	—	—	78	37
				II	90	—	139/26	—	—	—	125	35
				III	35	—	60/5	84	2.17	52.4	84	42
P. D.	29 F	M.S.	1.75	I	41	21	—	—	—	—	97	37
				II	60	38	—	—	—	—	103	34
				III	36	—	48/4	82	2.28	55.6	90	39
V. F.	40 F	M.S., A.I.	1.42	I	—	29	—	87	—	—	132	38
				II	60	40	—	120	2.00	86.2	150	36
				III	40	13	40/4	79	2.14	44.0	90	43
A. C.	44 M	A.I.	1.74	I	—	—	—	—	—	—	96	36
				II	56	—	78/15	88	2.24	78.3	100	38
				III	17	—	40/4	50	2.18	67.6	63	40
Normal Values					<20	<12	<30/5	<110	2.80–5.00	26.0–45.0	<100	26–35

M.S. = mitral stenosis
A.I. = aortic insufficiency
BSA = body surface area (M^2)
I = before pulmonary edema
II = during pulmonary edema
III = after recovery

PA_M = pulmonary artery mean pressure
PC_M = pulmonary wedge mean pressure
R.V. = right ventricular pressure (systolic and diastolic)
C.I. = cardiac index (L./min./M^2)
AV_{O_2} diff. = arteriovenous oxygen difference (ml./L.)
H.R. = heart rate (beats/min.)
D.F.P. = diastolic filling period (secs./min.)

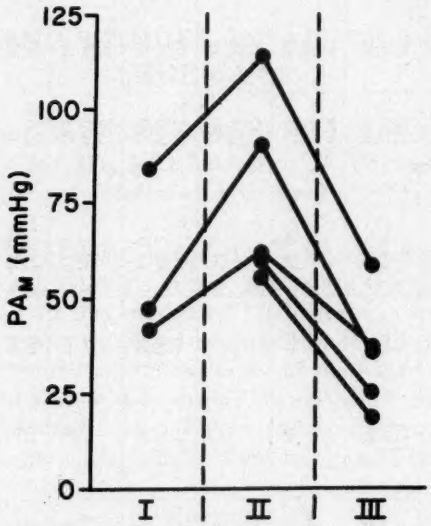


FIG. 1. Pulmonary artery (PA) mean pressures during control period (I), acute pulmonary edema (II), and recovery period (III) in three patients; and during periods II and III in two patients.

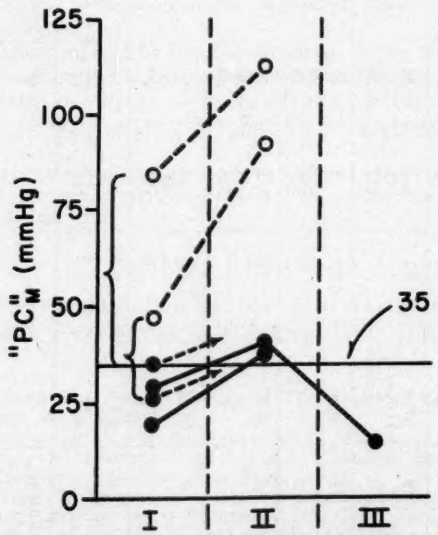


FIG. 2. Pulmonary wedge (PC) mean pressures, where measured, shown as closed circles. For two patients the PA mean pressures during periods I and II are shown as open circles bracketed with their corresponding PC mean pressures. The horizontal line at 35 mm. Hg pressure represents the approximate threshold of pulmonary edema.

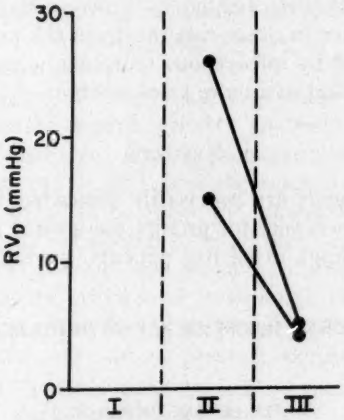


FIG. 3. Right ventricular end-diastolic pressures in two patients during pulmonary edema and after recovery.

insufficiency, and one had aortic insufficiency. All of these diagnoses were confirmed, at operation in four cases, and in one at autopsy. Four of the patients were catheterized during a period in which the effects of hexamethonium on pulmonary artery pressure were being investigated; hence this drug was ready for immediate administration.

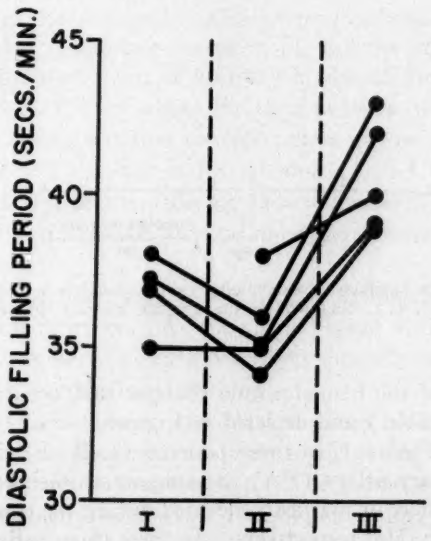


FIG. 4. Diastolic filling periods, expressed in seconds per minute, before, during, and after pulmonary edema.

These four patients were treated by intravenous hexamethonium bromide* given by catheter in doses ranging from 6.5 to 25 mg.; the remaining patient was treated by intravenous morphine, oxygen by mask, venous tourniquets, and elevation to a more erect position.

Results

Data on these patients are necessarily somewhat incomplete because of their distress and the necessity for prompt therapeutic measures. However, by combining the findings in all five patients, we hoped to obtain a fairly

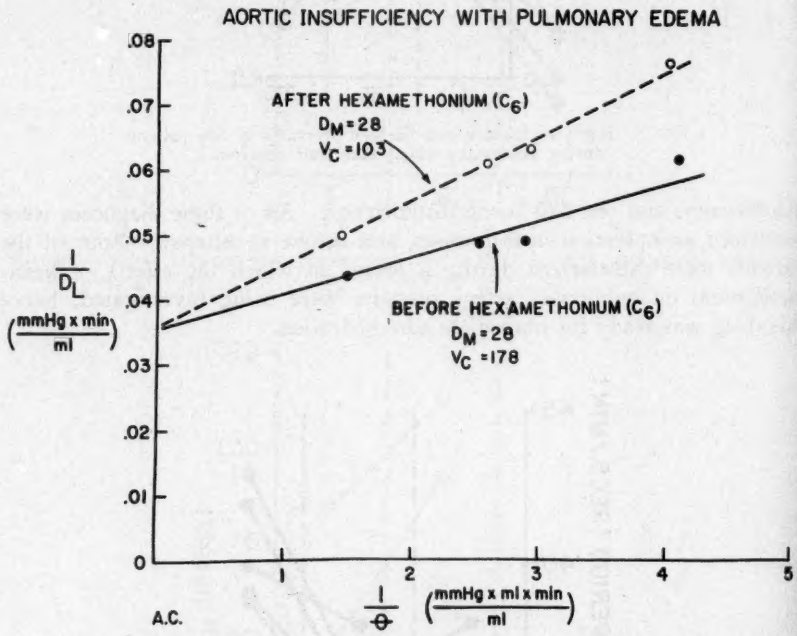


Fig. 5. Pulmonary capillary blood volume during pulmonary edema and after recovery in one patient (A. C.), obtained by the graphic method devised by Roughton and Forster.

complete picture of the hemodynamic changes that occurred. The results are presented in Table 1 and depicted in Figures 1–5.

As shown in Figure 1, in three patients (I. B., F. C., and P. D.) in whom the pulmonary artery (PA) pressure was measured, the mean pressures were moderately or markedly elevated during the control period, being 41, 47, and 84 mm. Hg, respectively. In these three patients the PA mean

* Courtesy of Burroughs Wellcome & Co., Tuckahoe, N. Y.

pressure rose significantly during pulmonary edema. In all five patients the PA pressure was considerably lower during the recovery period than during acute pulmonary edema.

The pulmonary wedge (PC) pressures were measured in all but one patient (H. C.) during the control period. The mean pressure varied from 21 to 35 mm. Hg (Figure 2). During pulmonary edema it was recorded in two patients (P. D. and V. F.), and the respective mean values of 38 and 40 mm. Hg were found to be above the approximate threshold of pulmonary edema (generally considered to be 35 mm. Hg). In one of these patients (V. F.) the PC pressure was measured during the recovery period and found to fall below the initial level. Although PC pressures were not obtained in two other patients during pulmonary edema, the rise noted in their corresponding pulmonary artery pressure suggests that the PC pressure would rise in a comparable fashion.

As indicated in Figure 3, the right ventricular end-diastolic (RV_D) pressure measured in two patients (F. C. and A. C.) during acute pulmonary edema was found to be considerably elevated (26 and 15 mm. Hg, respectively). During recovery the RV_D was within normal limits in three of four patients in whom the pressure was recorded.

During the control period the systemic artery mean pressure was measured in only two patients (I. B. and V. F.); it was slightly elevated in one. During pulmonary edema the systemic artery pressure rose in both patients. With the control of pulmonary edema the systemic artery pressure was within normal limits in all five patients.

The values of cardiac indices in general were low both during pulmonary edema and recovery. With one exception (I. B.) the cardiac index measured was below the lower limit of normal for our laboratory. In two patients (V. F. and A. C.) in whom the cardiac index was measured both during pulmonary edema and after recovery, there was no significant change. However, in these two patients and in another (I. B.) during pulmonary edema, there was a significant widening in arteriovenous blood oxygen difference associated with a parallel increase in oxygen consumption and minute ventilation.

In all patients the heart rate rose with the development of pulmonary edema and fell with recovery. As shown in Figure 4, the diastolic filling period in general was found to have decreased somewhat during pulmonary edema and to have increased on recovery.

Figure 5 shows the values of pulmonary capillary blood volume obtained in one patient in whom measurements were made during pulmonary edema and after treatment with hexamethonium. The pulmonary capillary blood volume during pulmonary edema was 102 ml./M^2, falling to 59 ml./M^2 on recovery. The normal range for our laboratory is 43.5 ± 11.3 ml./M^2 of body surface area.

Discussion

It is generally accepted that a pressure in the region of from 30 to 35 mm. Hg represents the level above which fluid will be forced through capillary walls in the lungs to produce edema, and this view is in keeping with our findings. However, we have studied other patients in whom PC pressures considerably above this level were not accompanied by pulmonary edema. It has been shown that continued elevation of PC pressures results in structural changes in the lung capillaries and alveolar septa,[6] and consequent tolerance of higher pressures before transudation occurs has been suggested.[3]

Changes in cardiac output in our patients are difficult to assess. In two patients the cardiac indices showed no significant change on recovery and all measured values were low. Although it is conceivable that on recovery from pulmonary edema the cardiac output would increase, it is also conceivable that the administration of hexamethonium might tend to reduce it, as a result of decreased venous return.

The work of Gorlin et al. has shown that a decreased diastolic filling period, such as occurs with tachycardia or with prolongation of ventricular systole, will further impair flow of blood through a stenosed mitral valve and may be a precipitating cause of pulmonary edema.[1]

The elevated right ventricular end-diastolic pressures found in two of our patients were associated with high PA pressures and presumably indicated incipient right ventricular failure. These elevated values must be reflected back into the right atrium and venae cavae.

It would appear that the precipitating causes of pulmonary edema in these patients were (1) the maintenance of a supine position for a prolonged period, with redistribution of blood from the peripheral circulation to the lungs, and (2) anxiety about the procedure, causing sympathetic stimulation. Sympathetic over-activity could cause tachycardia, with a consequent decreased diastolic filling period, and peripheral vasoconstriction, again with transfer of blood from the peripheral vessels to the pulmonary vascular bed.[7]

Because of the patients' distress the measurement of their oxygen consumption was difficult to accomplish, and here the advantages of the indicator dilution method of measuring cardiac output were manifest. In the last patient, who was exceedingly cooperative despite his distress, measurement of the diffusion capacity for carbon monoxide and pulmonary capillary blood volume was successfully achieved. A significant increase in pulmonary capillary blood volume during pulmonary edema suggests that the lung capillaries passively dilate with increase in intraluminal pressure.

In the four cases treated with intravenous hexamethonium, this agent produced a rapid and dramatic response, the changes being consistent with those reported in an earlier study done in this laboratory.[8] In contrast, the fifth patient, who was treated by intravenous morphine, oxygen, and venous tourniquets, improved much more slowly.

The exact mechanism of action of hexamethonium in these circumstances has not been completely elucidated. Reducing the total peripheral resistance, by reducing the load on the left ventricle, could relieve the congestion of the lungs in patients with hypertensive or aortic valvular disease. However, this action might not be expected to be as effective in patients with mitral stenosis except inasmuch as the reduction of left ventricular diastolic pressure would improve slightly the flow through the mitral valve. It seems more likely that in these patients reduction of venous return to the right heart due to decrease in venous tone and pooling of blood in the peripheral venous system, with a consequent temporary reduction in right heart output, is the principal cause of their improvement. The role of the systemic veins in the genesis of pulmonary edema has been the subject of an excellent review by Sarnoff,[9] and the above theories of action of hexamethonium in relieving it have been advanced also by other workers.[10, 11]

A rise in venous pressure tends to cause an increase in heart rate; conversely a fall in venous pressure results in a decrease in heart rate,[12] which in turn produces a lengthening of the diastolic filling period. For a given cardiac output this means a lower mitral valve flow rate, a lower pressure gradient across the valve, and a consequent reduction in left atrial and pulmonary capillary pressure.

It has been suggested that the pulmonary veins have the capacity to constrict[13] and, if this did in fact occur in pulmonary edema, relaxation of such venoconstriction due to the action of hexamethonium would reduce PC pressure. Our data do not prove or disprove any direct effect of hexamethonium on the pulmonary veins, since comparison of simultaneous left atrial and PC pressures would be necessary for this.

Summary

Hemodynamic changes are described in five patients, before, during, and after episodes of acute pulmonary edema.

The principal findings included a marked rise in pulmonary artery and pulmonary wedge pressures, low cardiac output, increased heart rate, and decreased diastolic filling period. Marked elevation of systemic blood pressure and increase in right ventricular diastolic pressure were observed in two patients.

Four patients were treated with intravenous hexamethonium in doses ranging from 6.5 to 25 mg. and all showed a dramatic response to the drug with regression of the above changes and prompt clinical improvement.

Summario in Interlingua

Le alterationes hemodynamic esseva studiate que occurreva in cinque patientes con sever morbo valvulo-cardiac in qui acute edema pulmonar se disveloppava durante le effectuation de catheterismo cardiac. Le declaration del edema pulmonar esseva evidentiate per formas acute de dyspnea, tusse, angustia mental, e le disveloppamento de ronchos in omne partes del campos pulmonar.

Le valores medie del tension pulmono-arterial esseva elevate per grados moderate o marcate durante le periodo de controlo. Iste valores montava significativemente durante le edema pulmonar e redescendeva durante le restablimento. Le tensiones a cuneo pulmonar esseva 21 a 35 mm de Hg al initio, e in le duo patientes in qui iste tensiones poteva esser registrate durante le edema pulmonar illos attingeva un nivello de 38, respectivemente de 40 mm de Hg, i.e., illos excedeva le limine approximative del transsudation ab le vasculatura capillar. Le tensiones termino-diastolic del ventriculo dextere esseva considerabilemente augmentate durante le phase acute del edema pulmonar e se trovava intra le limites del norma post le restablimento ab le edema in tres inter le quatro patientes in qui illos poteva esser determinate. Le tension del arterias systemic montava con le declaration del symptomas e retornava a nivellos intra le limites del norma como effecto del tractamento. Le indices cardiac, a generalmente parlar, esseva basse. In omne le patientes, le frequentia cardiac montava con le disveloppamento del edema pulmonar e redescendeva con le restablimento. Per consequente, le periodo de replenation diastolic decresceva generalmente con le edema e montava con le restablimento. Le volumine de sanguine pulmono-capillar que esseva determinate in un del patientes amontava a 102 ml/m² durante le edema pulmonar e a 59 ml/m² durante le restablimento post therapia a hexamethonium.

Il pare que le causas precipitatori del edema pulmonar in nostre patientes esseva le prolongate mantenentia de un decubito dorsal con le possibile effecto de un redistribution de sanguine ab le peripheria ad le pulmones e le stato de anxietate con le effecto de un hyperactivitate del systema nervose sympathic. Iste ultime condition causarea tachycardia, abbreviation del periodo de replenation diastolic, e vasoconstriction peripheric.

Quatro del patientes esseva tractate con hexamethonium per via intravenose, con le effecto de un rapide e frappante restablimento ab le acute edema pulmonar. Nos ha permittite nos varie speculationes relative al mechanismo del action de iste droga in tal casos. Le reduction del resistentia peripheric total, per reducer le cargation del ventriculo sinistre, pare apte a alleviar le congestion del pulmones in patientes con morbo cardiac hypertensive o de valvula aortic. In casos de stenosis mitral, il pare probabile que un effecto major del droga consiste in le reduction del retorno venose al corde dextere in consequentia de un reduction del tono venose e de un accumulation de sanguine in le systema venose peripheric. Altere modos possibile del action de hexamethonium es discutite.

BIBLIOGRAPHY

1. Gorlin, R., Lewis, B. M., Haynes, F. W., Spiegl, R. J., Dexter, L.: Factors regulating pulmonary "capillary" pressure in mitral stenosis. IV. Amer. Heart J. **41**: 834, 1951.
2. Lenegre, J., Scebat, L., Benchemont, F., Damien, J.: Étude de la pression capillaire pulmonaire dans differents types de cardiopathies. Arch. Mal. Coeur. **46**: 1, 1953.
3. Hayward, G. W.: Pulmonary oedema. Brit. Med. J. **1**: 1361, 1955.
4. Fejfar, Z., Fejfarova, M., Bergmann, K., Brod, J.: Haemodynamic changes during acute pulmonary oedema. Cardiologia **34**: 233, 1959.
5. Roughton, F. J. W., Forster, R. E.: The relative importance of diffusion and chemical reaction rates in determining the rate of exchange of gases in the human lung, with special reference to the volume of blood in the lung capillaries and the true diffusing capacity of the pulmonary membrane. J. Appl. Physiol. **11**: 290, 1957.
6. Parker, F., Jr., Weiss, S.: The nature and significance of the structural changes in the lungs in mitral stenosis. Amer. J. Path. **12**: 573, 1936.
7. Sarnoff, S. J., Sarnoff, L. C.: Neurohemodynamics of pulmonary edema. I. Autonomic influence on pulmonary vascular pressures and the acute pulmonary edema state, a preliminary report. Dis. Chest. **22**: 685, 1952.

8. Yu, P. N., Nye, R. E., Jr., Lovejoy, F. W., Jr., Schreiner, B. F., Yim, B. J. B.: Studies of pulmonary hypertension. IX. The effects of intravenous hexamethonium on pulmonary circulation in patients with mitral stenosis. J. Clin. Invest. **37**: 194, 1958.
9. Sarnoff, S. J.: Some physiologic considerations in the genesis of acute pulmonary edema. Pulmonary Circulation, p. 273, Grune & Stratton, New York, 1959.
10. Werkö, L., Frisk, A. R., Wade, G., Eliasch, H.: Effect of hexamethonium bromide in arterial hypertension. Lancet **2**: 470, 1951.
11. Kelley, R. T., Freis, E. D., Higgins, T. F.: The effects of hexamethonium on certain manifestations of congestive heart failure. Circulation **7**: 169, 1953.
12. Bainbridge, F. A.: The influence of venous filling upon the rate of the heart. J. Physiol. **50**: 65, 1915.
13. Burch, G. E., Romney, R. B.: Functional anatomy and "throttle valve" action of the pulmonary veins. Amer. Heart J. **47**: 58, 1954.

IS BRUCELLOSIS IMPLICATED IN CALCIFIC AORTIC VALVULAR STENOSIS? *

By GEORGE C. GRIFFITH, M.D., F.A.C.P., and H. THOMAS NORRIS, M.D.,
Los Angeles, California

ALTHOUGH calcific aortic stenosis is generally accepted to be a late sequela of rheumatic fever, several factors suggest that rheumatic fever may not be the sole or even the principal cause of the valvular deformity. First, a history of joint disease is present in only 20 to 30% of patients with aortic stenosis. Second, the valvular lesion is usually more severe than would be expected if rheumatic fever were the cause. Third, the reported sex incidence (three male patients to each female patient) is not what would be anticipated if rheumatic fever were responsible, inasmuch as rheumatic fever is rather evenly divided between the sexes.

TABLE 1

Incidence of Cardiovascular Manifestations During Brucellosis
(Review of Recent Literature)

Investigator	No. of Cases Studied	Incidence of Cardiovascular Disease No. of Cases	History of Rheumatic Fever
Spink[1]	244	13	2
Posteli, Atlanta, Rosa[2]	75	53	—
Moeschlin[3]	34	11	—
Amuchastegui[4]	116	108	—
Maldonado-Allende[5]	428	55	—
Poli[6]	166	56	—
Panuccio[7]	137	25	3
Perry, Evans[8]	10	10	1
Grant, Stone[9]	1	1	—

Over the years, frequent mention has been made of the involvement of the cardiovascular system in brucellosis. The number of cases studied and the incidence of cardiovascular disease reported therein are summarized in Table 1.

In 1956, Perry [10] presented evidence that calcific aortic stenosis might be a late manifestation of brucellosis, and in later publications Perry alone [11] and with Evans [8] suggested that brucellosis even may be the chief cause of calcific aortic stenosis.

In light of these reports we reviewed the hospital charts at the Los Angeles County Hospital in order to detect a possible relationship between

* Received for publication July 7, 1960.
From the University of Southern California School of Medicine and the Los Angeles County General Hospital, Los Angeles, California.
Requests for reprints should be addressed to George C. Griffith, M.D., 1136 West Sixth Street, Los Angeles 17, California.

brucellosis and aortic stenosis. Our approach to this problem was two-fold. First, we examined the hospital charts of 144 patients (107 men and 37 women) with proved cases of brucellosis who were treated at the Los Angeles County Hospital in the decades 1928–1938, 1938–1948, and 1948–1958 for recorded evidence of aortic stenosis. The diagnosis of brucellosis was considered "proved" if blood cultures were positive for *Brucella abortus,* (19 instances), *B. melitensis* (1 instance), or *B. suis* (two instances), and if a four-fold rise in antibody titers were present, or both. The second step was to examine the hospital records of all patients 50 years of age and over in whom calcific aortic stenosis was found at autopsy during the period 1918–1948, to determine whether the valvular deformity could have resulted from brucellosis.

In the period between August, 1928 and July, 1958, 107 men and 37 women were treated for brucellosis at the Los Angeles County Hospital. Of these, 134 (93%) were Caucasians, and 10 (7%) were Negroes. The disease occurred somewhat earlier in the men than in the women, the average age of onset being 31.8 years for the men and 40.4 years for the women. Despite a painstaking search of their records, we have been unable to uncover a single instance in which clinical symptoms or signs of aortic stenosis are recorded for any of the 144 patients during the acute illness or at any subsequent hospitalization, although we have been able to follow 29 of these patients for over seven years from the onset of the disease. Six of the 144 patients are known to be dead. Two of them have come to autopsy at this hospital; neither one had the pathologic finding of calcific aortic stenosis.

In the years 1918–1948, 275 patients over the age of 50 had autopsy findings of calcific aortic stenosis. Two hundred twelve of the 275 (77%) were men; 63 (23%) were women. Not one of these patients had a past history of brucellosis.

In summary, we have been unable to determine any etiologic relationship between brucellosis and calcific aortic stenosis in an analysis based upon the study of 144 proved cases of brucellosis and the study of 275 autopsied cases of calcific aortic stenosis.

Summario in Interlingua

Perry suggereva que calcific stenosis aortic es possibilemente un sequella tardive de brucellosis e mesmo que brucellosis pote esser un causa principal de iste lesion. Le scrutinio del documentation hospitalari de 107 masculos e 37 femininas tractate pro brucellosis al Hospital del Contato Los Angeles inter 1928 e 1958 revelava nulle allusion a calcific stenosis aortic. Nulle anamnese de brucellosis esseva notate in ulle del casos de 212 masculos e 63 femininas de etates de plus que 50 annos con constatationes de calcific stenosis aortic pro qui necropsias esseva executate al mentionate hospital inter 1918 e 1948. Sex del 144 patientes con brucellosis es cognoscitemente morte. Duo de illes esseva necropsiate a iste hospital. Nulle del duo habeva constatationes de calcific stenosis aortic. Le conclusion es que nostre datos non permitte le postulation de un relation etiologic inter brucellosis e calcific stenosis aortic.

BIBLIOGRAPHY

1. Spink, W. W.: The nature of brucellosis. The University of Minnesota Press, Minneapolis, 1956.
2. Posteli, T., Atlanta, G., Rosa, L.: Un caso di endocardite ulcerosa di natura melitococcica. Cuore e circol. **27**: 117 (Apr.) 1943.
3. Moeschlin, S.: Elektrokardiographische Myokardschaden bei der Febris undulans Bang. Cardiologia **7**: 29, 1943.
4. Amuchastegui, S. R.: Las enfermedades cardiovasculares en el curso de la brucelosis. Rev. Asoc. med. Argent. **62**: 137, 1948.
5. Maldonado-Allende, I.: Aspectos clinicos de la brucelosis cardiovascular. Prensa med. Argent. **35**: 2323, 1948.
6. Poli, M.: L'apparato cardiovascolare nella brucellosi. Omnia med., 1953.
7. Panuccio, P.: Brucella myocarditis: observations on patients reported in the literature and on a group of patients seen in the past 10 years in the medical clinic of the University of Florence. Abstracted in J. A. M. A. **165**: 1496 (Nov. 16) 1957.
8. Peery, T. M., Evans, J. M.: Brucellosis and heart disease. III. Chronic valvular heart disease following nonfatal brucellosis. Ann. Intern. Med. **49**: 568 (Sept.) 1958.
9. Grant, G. H., Stone, C. L.: Rupture of the heart as result of brucellosis abortus endocarditis. Brit. Med. J. **1**: 914, 1953.
10. Peery, T. M.: Brucellosis and heart disease. I. The shaky foundations of "rheumatic" heart disease. Postgrad. Med. **19**: 323 (Apr.) 1956.
11. Peery, T. M.: Brucellosis and heart disease: IV. Etiology of calcific aortic stenosis. J. A. M. A. **166**: 1123 (Mar. 8) 1958.

EFFECTS OF EXCESS SODIUM CHLORIDE ON BLOOD LIPIDS: A POSSIBLE FACTOR IN CORONARY HEART DISEASE * †

By G. Douglas Talbott, M.D., John R. Keys, M.D., Bessie M. Keating, M.T. (ASCP), and Beatrice Finkelstein, M.S. (Nutrition), *Dayton, Ohio*

Although sodium chloride is an essential constituent of every living cell, in man the amount ingested appears to be dictated by conditions other than metabolic need. Diets throughout the world vary greatly in their salt content; whether or not more salt is added seems to be determined solely on the basis of palatability. Some investigators feel that palatability in turn depends chiefly upon habit,[1] while others maintain that it is an inherent quality of the food itself.[2-4]

History shows that the further a group's customs depart from the primitive, the greater is the desire for salt as a seasoning. Primitive man did not add salt to his food so long as he either lived by the sea or ate his meat raw. Even when fire was first tamed for cooking, salt was not needed because meat that had been roasted retained sufficient sodium chloride to satisfy the unsophisticated palate. But the next progressive change in diet did make salt desirable, since both boiled meat and cereal foods require salt for savor.[4] Sociologists have noted that through the ages the use of salt has consistently increased with each move inland, with each advance in cereal consumption, and with each new wave of urbanization—in short, with the progress of civilization.[2] Even now it is said that many Eskimos add no salt at all to their food,[4] and that some African tribes use less than two grams per day.[5]

The picture is quite different in the more progressive societies. In a recent study of a random group of Americans, for example, Dahl found a daily salt intake of up to 24 gm., and concluded that the average American male consumes 10 gm. per day;[6] other investigators have sometimes put the figure even higher.[3] Even the more conservative calculation places our average salt consumption at least eight grams in excess of estimated metabolic requirements,[7, 8] and easily makes table salt our most common dietary additive. One wonders if it is mere chance that both the use of sodium chloride and the incidence of coronary heart disease have increased hand in hand with the rising tide of progress, not only in present but in past civilizations as well.

* Received for publication April 1, 1960.
† This work was supported by Contract No. AF 33 (616)-6331, USAF.
Requests for reprints should be addressed to G. Douglas Talbott, M.D., Medical Director, American Medical Research Foundation, 1230 Fidelity Medical Building, Dayton 2, Ohio.

Now, with increasing suspicion being directed toward the role of hyperlipidemia in the etiology of coronary heart disease, it has become desirable to investigate all alterable factors which might contribute to the hyperlipemic state. Although sodium chloride is a logical candidate for such investigation, medical literature contains only meager reference to the effect of salt on fat metabolism, and the available information is based principally on a few animal experiments which may or may not be directly applicable to man. A project was therefore designed specifically to permit observation of the effect of ingested sodium chloride on each of several blood values in man, and particularly on the clearance time of artificially elevated blood fat.

Material and Methods

The subjects were 20 apparently normal males from a nearby prison farm, whose ages ranged from 18 to 39 years. The men were chosen from a group of volunteers. After their good health was confirmed by a medical examination they were placed in solitary confinement and given a pre-cooked, pre-frozen diet that had been analyzed for its nutritional content (Table 1).

Table 1

A Nutritional Analysis of the Diet

	Calories	Protein (gm.)	Fat (gm.)	Carbohydrate (gm.)	Calcium (mg.)	Iron (mg.)	Vit. A, I.U.	Thiamin (mg.)	Riboflavin (mg.)	Niacin (mg.)	Ascorbic acid (mg.)	Fiber (gm.)	Sodium (mg.)
Average per day	3,038	112.7	142.4	335.7	1,108.5	21.7	8,090	1,508	2,395	19.9	69.3	4.1	4,126
Recommended daily allow.	3,200	70.0	—	—	800	12	5,000	1,600	1,600	16.0	75.0	—	4,000

While thus confined, the men did calisthenics for 10-minute periods twice each day. Since it was intended that each man should serve as his own control, careful individual records of weight, water consumption, and food consumption were kept from the beginning.

During the first week the diet contained an ordinary amount of table salt, i.e., an average of 4.126 gm. per day (Table 1). At the end of the week, fasting blood was drawn to determine the individual values of: (1) total cholesterol, using method described by Zak et al.;[9] (2) cholesterol esters; (3) phospholipids, after method of Youngsberg;[10] (4) athero-index; (5) total lipids, total lipid turbidity determined as described by Kunkel;[11] (6) total esterified fatty acids, using method described by Stern and Shapiro;[12] (7) neutral fatty acids; (8) beta lipoproteins; and (9) alpha lipoproteins, using method of paper electrophoresis described by Straus and Wurm.[13] As an ancillary project, coagulation times as determined by the silicone method were also studied.

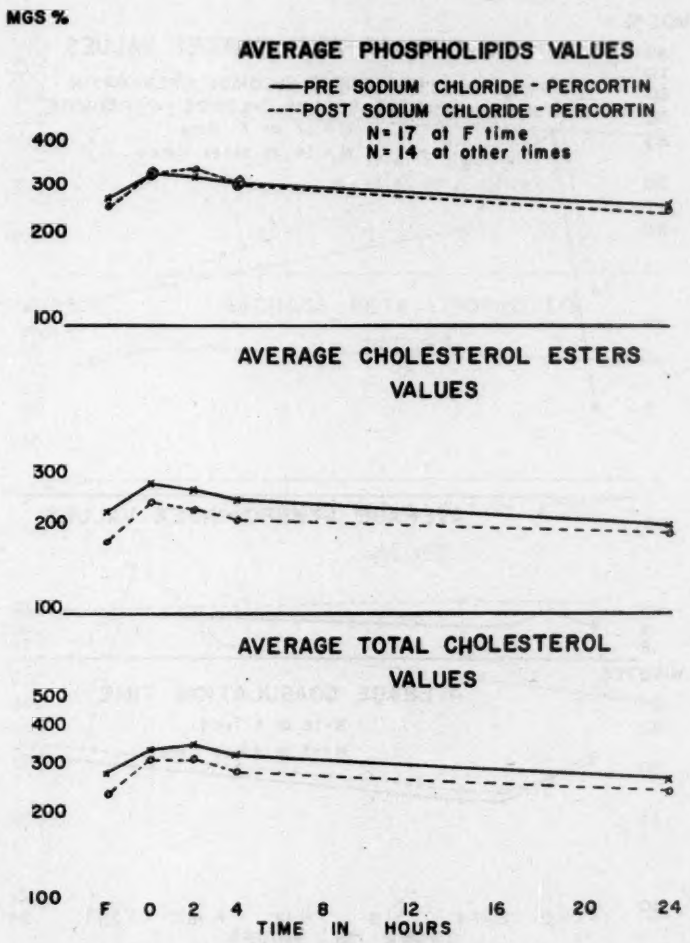


FIG. 1. Comparison of average values before and after sodium chloride-Percortin for phospholipids, cholesterol esters, and total cholesterol.

After these initial determinations were made, the blood fat was artificially elevated by injecting Lipomul, 5 ml./Kg. of body weight, into the blood stream of each subject. Blood lipid clearance time was then calculated by determining the respective values of the above-listed blood lipid factors immediately after infusion and again at two, four, and 24 hours thereafter. In this manner an individual control time was established for each factor.

During the second week of the experiment, the conditions of the first week were repeated exactly, except that each man was given (1) sodium chloride, 20 gm. per day in four divided doses of enteric-coated tablets, and

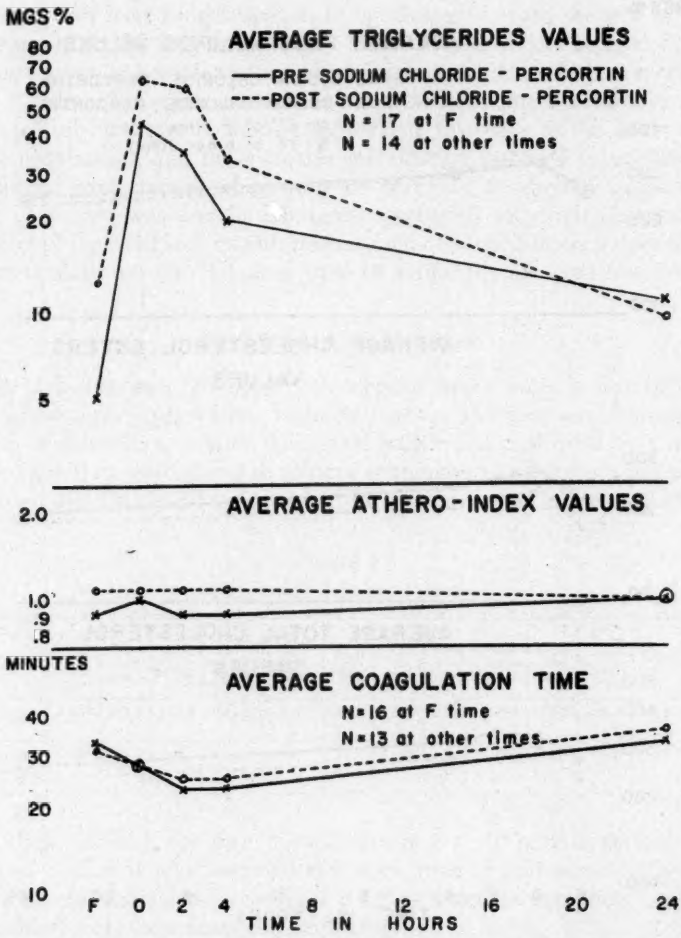


FIG. 2. Comparison of average values before and after sodium chloride-Percortin for triglycerides, athero-index, and coagulation time.

(2) Percortin, 5 mg. per day, the latter for the purpose of inhibiting the urinary excretion of salt.

After a week of the sodium chloride-Percortin regimen, fasting blood values were again obtained, Lipomul was again injected, and lipid factors were determined as before, at zero, two, four, and 24 hours after Lipomul.

Individual blood clearance times at the end of the second week were then compared with those of the first week to discover the effect of added salt. The accompanying graphs (Figures 1, 2, 3) compare the average blood values of the group as a whole, before and after the sodium-Percortin regimen.

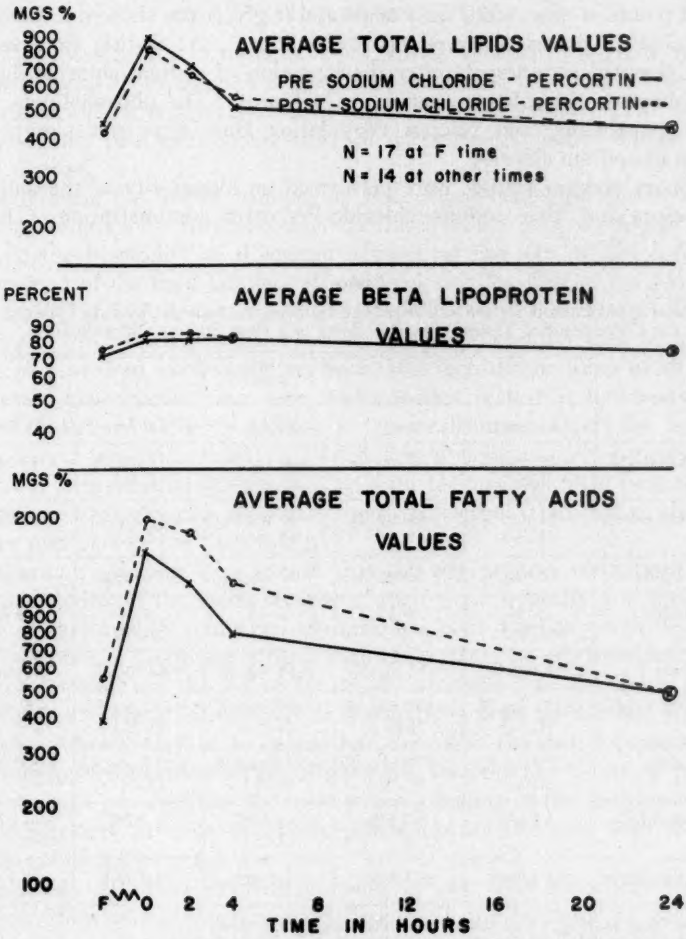


FIG. 3. Comparison of average values before and after sodium chloride-Percortin for total lipids, beta lipoproteins, and total fatty acids.

RESULTS AND STATISTICAL EVALUATION

Of the nine blood factors measured, only four showed statistically significant response to sodium chloride at any time. Statistical analysis was based on the determination of whether changes as great or greater in either direction (plus or minus) as those observed would be likely to occur five or more times per hundred, due to sample variation, in repeated experiments of this size. Therefore, in Table 2 the legend "L. S." (likely significant) carries a confidence coefficient of 95%, which is the standard "p" constant. On this basis, cholesterol and cholesterol esters showed a significant decrease

at most points in time, while fatty acids and triglycerides showed a consistent increase at all points observed up to 24 hours. At fasting time several factors changed significantly after the ingestion of sodium chloride, but no factor showed a significant change at 24 hours. The phospholipids, total lipids, lipoproteins, and silicone coagulation time were not significantly affected by sodium chloride.

Urinary sodium studies were performed on a majority of the subjects, both before and after sodium chloride-Percortin administration. Despite

TABLE 2

Blood Lipid Factors Before and After the Infusion of Lipomol: Average Changes at Corresponding Times After One Week of a High Sodium Chloride Diet

Blood Factor	Time				
	Fasting	Zero	2 Hours	4 Hours	24 Hours
Total cholesterol	−40 mg.% (L.S.)	−30 mg.%	−34 mg.% (L.S.)	−42 mg.% (L.S.)	−17 mg.%
Cholesterol esters	−41 mg.% (L.S.)	−38 mg.% (L.S.)	−40 mg.% (L.S.)	−38 mg.% (L.S.)	−10 mg.%
Phospholipids	−12 mg.%	−2 mg.%	−10 mg.%	No change	−10 mg.%
Athero-index	+.14 (L.S.)	+.11	+.12	+.14 (L.S.)	+.02
Total lipids	−8 mg.%	−55 mg.%	−38 mg.%	+42 mg.%	+1 mg.%
Total fatty acids	+173 mg.% (L.S.)	+440 mg.% (L.S.)	+607 mg.% (L.S.)	+414 mg.% (L.S.)	−6 mg.%
Triglycerides	+7.3 mg.% (L.S.)	+19.1 mg.% (L.S.)	+23.6 mg.% (L.S.)	+13.0 mg.% (L.S.)	−6.0 mg.%
Beta lipoproteins	+1.4%	+2.6%	+3.35% (L.S.)	+.07%	−1.1%
Coagulation time	−1.4 min.	−.3 min.	+1.4 min.	+2.4 min.	−1.4 min.

N = 16 at fasting, 13 at other times, for coagulation time.
N = 17 at fasting, 14 at other times, for all other blood factors.
L.S. = Likely significant ($p < .05$).

the increased oral intake of sodium, there was an average decrease of 45 mEq./L. of sodium chloride in the urine. Although there was no direct measurement of total serum sodium, it was assumed from these values that the total serum sodium pool had expanded.

Control studies run on Lipomul alone revealed no statistically significant change when repeated on two successive weeks. Control studies designed to explore the differential between Lipomul and Percortin, and between Lipomul and sodium chloride indicated that none of these variables statistically affected the validity of the results originally obtained.

Discussion

With these results in mind, a review of the literature suggests that two pertinent areas of investigation have been somewhat neglected. One is the importance of the triglycerides as a factor in atherogenesis. The other is the possibility of a relationship between excessive salt intake and coronary heart disease.

Only since the use of isotopes as tracers and the development of biochemical technics for further analytical fractionation have we begun to appreciate the possibility of divergent actions on the part of the individual components of the lipid family. Cholesterol was the first of the lipid fractions to be identified, measured, and studied in the laboratory. Perhaps because of this priority, perhaps because of the comparative ease with which it can be measured, cholesterol has been until recently the focus of attention. However, experiments have now demonstrated that it is most unwise to accept cholesterol alone as a basis for generalizations about the behavior of lipids as a whole.[14] It seems possible that many past discrepancies in the results of experimental studies dealing with fat analysis were basically due to a failure to distinguish the behavior of cholesterol from that of the more elusive members of the lipid family.

Although we have long known that the triglycerides constitute an important fraction of the lipids because of their great quantity and their wide range of variability,[15] comparatively little has been done as yet to determine their behavior. There are strong indications that the triglycerides, rather than cholesterol, are the active factors in whatever role the lipids play in atherogenesis. In a recent study of the lipids in both normal and coronary subjects, Albrink and Man found that the most obvious differential was the consistently elevated serum triglyceride level in the coronary group.[16] Bottcher et al. reported that the most striking finding in the analysis of lipids in the coronary arteries of elderly atherosclerotic subjects was the high percentage of triglycerides.[17]

Probably the most impressive result of our own experiment was its demonstration of the conspicuous difference in the behavior of cholesterol as opposed to the triglycerides in response to increased sodium chloride. Both cholesterol and cholesterol esters fell, while both the total fatty acids and the triglycerides rose to significantly higher levels. This observation points to the second area not previously explored.

Although for many years it has been customary to recommend salt restriction in the treatment of both hypertension and congestive heart failure, there has been little or no attempt to investigate the possibility of a relationship between excessive salt consumption and coronary heart disease. That there may well be such a relationship was suggested by the outcome of some experiments with rats as reported by Bavetta et al. several years ago.[18] These workers found that although adrenalectomy normally caused the rate of fat absorption to fall about 38%, if the adrenalectomized animals were

given a salt solution the rate of fat absorption fell only about 24%. The results of later experiments with rats, published by Meneely and Ball in 1958,[19] strengthen the indications of such a relationship, for they found that when dietary salt was increased to amounts as great as 7% and continued for as long as two months, the results were disturbed lipid metabolism and the deposition of lipids in arterioles throughout the body.

If the deposition of lipids and disturbance in lipid metabolism are important factors in atherogenesis, then the restriction of any nonessential element which contributes to such conditions would appear to be a logical step in controlling the disease. At least one investigator [20] has expressed the opinion that the most effective time to apply restriction to salt intake is during youth. This would suggest that limiting the ingestion of salt early in life might serve as a prophylactic measure for those whose family history or individual constitution indicates a special tendency toward atherosclerosis. This concept so far remains purely in the realm of speculation, but at least it challenges exploration.

While it must be pointed out that no clinical conclusions are as yet warranted from our study, the statistical significance of the variations in response displayed by the various lipid fractions appears to justify further investigation of the effect of excess sodium chloride on the blood lipids of man. If other workers, dealing with human subjects, independently determine fractional lipid levels comparable to those reported by Albrink and Man, and by Bottcher et al., then we may more strongly suspect that the triglycerides are one of the most active lipid factors in atherogenesis. If additional investigations confirm our own observation that sodium chloride depresses cholesterol and elevates the triglycerides, it would certainly suggest that early limitation of salt intake might offer a means of helping to control atherosclerosis.

Summary and Conclusions

Changes in blood lipids were measured in 20 healthy men following an infusion of Lipomul given before and after a week during which time the subjects were given 20 mg. of extra sodium chloride per day.

Comparison showed that both cholesterol and cholesterol esters were depressed at most points in time observed, except at the 24-hour post-Lipomul point; serum triglycerides and fatty acids were significantly increased at the corresponding times. All other blood values remained essentially unchanged. Differentiations found at fasting times were in no instance reflected 24 hours after Lipomul.

Though clinical conclusions are not yet warranted, the statistical significance of the fractional lipid variations noted in this experiment may indicate the desirability of restricting excessive intake of sodium chloride as a means of controlling coronary heart disease. Further investigation of this possibility appears justified.

ACKNOWLEDGMENT

The authors are greatly indebted to Colonel John P. Stapp, Dr. Frederick Berner, and Dr. Edwin Hiatt of the Aerospace Medical Laboratory, for their helpful criticism. We also wish to express appreciation to Mr. Darwin Palmari for the statistical analysis, and to Dr. James Funkhouser of Miami Valley Hospital for his contribution on determining blood-clotting times.

SUMMARIO IN INTERLINGUA

Vinti prisioneros qui esseva clinicamente normal se presentava voluntarimente a servir como subjectos del presente studio. Illes esseva placiate in cellulas solitari e recipeva durante un septimana un nutritionalmente analysate dieta que contineva un quantitate moderate de sal. Alora, post un infusion de Lipomul, le tempores individual del clearance sanguinee esseva determinate pro plure fractiones lipidic in stato jejun, al tempore zero, e post duo, quatro, e 24 horas. Cata un del homines serviva como su proprie subjecto de controlo.

Durante le secunde septimana, le mesme conditiones ambiente esseva mantenite, sed omne participante recipeva 20 g de chloruro de natrium per die, con Percortina supplemental. Al termino del septimana le infusion de Lipomul esseva repetite e le tempores del clearance sanguinee esseva determinate como previemente.

Le comparation del duo series de datos monstrava que post le dieta a chloruro de natrium, le valores pro cholesterol e etiam pro esteres de cholesterol in le sanguine esseva deprimite, durante que le valores pro acidos grasse e etiam pro triglyceridos esseva uniformemente elevate a omne periodos de observation con le exception de illo de 24 horas. Omne le altere valores del sanguine remaneva essentialmente non-alterate.

Ben que le formulation de conclusiones clinic es non ancora justificate, le signification statistic del constatate variationes in le fractiones lipidic hic studiate suggere investigationes additional relative al rolo de chloruro de natrium in le metabolismo del lipidos individual, specificamente in tanto que illo es possibilemente relationate con le disveloppamento de morbo de arteria coronari.

BIBLIOGRAPHY

1. Kaunitz, H.: Causes and consequences of salt consumption. Nature **178**: 1141, 1956.
2. Eckel, E. C.: *Salt,* Encyclopedia of the Social Sciences. Edited by E. Seligman. The Macmillan Co., New York, Vol. 13, pp. 522–526, 1955.
3. Sherman, H. C.: Chemistry of food and nutrition, 8th ed. The Macmillan Co., New York, pp. 232–233, 1952.
4. Meneely, G. R.: Salt. Amer. J. Med. **16**: 1, 1954.
5. Dahl, L. K.: Salt intake and salt need (part I). New Engl. J. Med. **258**: 1152, 1958.
6. Dahl, L. K.: Sodium intake of the American male; implications on etiology of essential hypertension. Amer. J. Clin. Nutrition **6**: 1, 1958.
7. Bourne, G. H., Kidder, G. W., Editors: Biochemistry and physiology of nutrition. Academic Press, New York, Vol. II, p. 535, 1953.
8. Krause, L.: Salt. Maryland Med. J. **1**: 277, 1952.
9. Zak, B., et al.: Total and free cholesterol. Amer. J. Clin. Path. **24**: 1307, 1954.
10. Hawk, P. B., et al.: Practical physiological chemistry, 13th ed. Blakiston Co., New York, pp. 589–590 and 633–634, 1954.
11. Kunkel, H. G., et al.: Application of turbidimetric methods for estimation of gamma globulin and total lipid to the study of patients with liver disease. Gastroenterology **11**: 499, Oct. 1948.
12. Stern, I., Shapiro, B.: Rapid and simple method for determination of esterified fatty acids and for total fatty acids in blood. J. Clin. Path. **6**: 158, 1953.

13. Straus, R., Wurm, M.: A new staining procedure and a method for quantitation of serum lipoproteins separated by paper electrophoresis. Tech. Bull. Regist. Med. Techn. **28**: 89, 1958.
14. Keating, B. M.: The relationship of serum cholesterol to blood lipid patterns. Amer. J. Med. Techn. **23**: 312–320 (Sept.–Oct.) 1957.
15. Gould, R. G.: Lipid metabolism and atherosclerosis. Amer. J. Med. **11**: 209, 1951.
16. Albrink, M. J., Man, E. B.: Serum triglycerides in coronary artery disease. Arch. Intern. Med. **103**: 4, 1959.
17. Bottcher, C. J. F., et al.: Composition of lipids isolated from the aorta, coronary arteries and circulus willisii of atherosclerotic individuals. Nature **183**, p. 47, 1959.
18. Bavetta, L., et al.: The effect of adrenalectomy on fat absorption. Amer. J. Physiol. **134**: 619, 1941.
19. Meneely, G. R., Ball, C.: Experimental epidemiology of chronic sodium chloride toxicity and the protective effect of potassium chloride. Amer. J. Med. **25**: 713, 1958.
20. Meneely, G. R.: Salt. Amer. J. Med. **16**: 31, 1954.

LEG ACHE: A SYMPTOMATIC INDICATION OF IRREGULAR GOUT *†

By HERMAN PEPPER, M.D. and LOUIS MANN, M.D.,
Redwood City, California

THE clinical, biochemical, and histiologic manifestations of typical gout have been described extensively, and the diagnosis is usually made without difficulty. The differential diagnosis of irregular or atypical gout, however, continues to be a problem. Irregular gout has many signs and symptoms which are not characteristic of typical gout. It is insidious in onset, causes mild arthritis, usually affects women, and progresses slowly without remission. A family history of the disease is rarely elicited. Tophi are absent.[1] Serum uric acid levels are at the upper limits of normal or slightly higher. The diagnosis can only be made by demonstrating sodium urate deposits in the tissues or by the patient's prompt and favorable response to colchicine.[1]

The purpose of this report is to describe the clinical records of nine patients in whom the only symptom was myalgia in the thigh and calf muscles, a symptom eventually proven to be a manifestation of gout.

CASE REPORTS

Case 1. A 48-year-old physician had had dull and persistent pain in both calves and thighs, recurring every three or four months, for 15 years. The pain began shortly after arising, persisted all day, and was relieved only by complete rest. It was aggravated by standing and walking, and usually subsided gradually after three or four weeks' duration. At no time did joint pain or stiffness occur. The muscles of both legs were sensitive to pressure. Self treatment with analgesics gave poor results. When attacks of leg ache continued, an orthopedist, an internist, a neurologist, and a neurosurgeon were consulted in succession, but all were unable to demonstrate any pathologic changes. The patient was hospitalized for studies; renal and hepatic function tests, a hematologic survey, and a spinal fluid examination revealed no abnormal findings. Following one particularly severe attack of leg ache, physical examination again was negative, but the serum uric acid level was noted to be 6.5 mg.% (normal according to Folin-Newton method: 2.6 to 6.0 mg.%.) No tophi were present, and a family history of gout was denied, but nevertheless irregular gout was suspected. Treatment with colchicine (total dose, 7.2 mg.) was initiated, followed by probenecid (Benemid, 1 gm. daily). The patient had prompt relief from leg ache for the first time, and the serum uric acid level decreased to 3.7 mg.% within eight days and within two weeks to 2.9 mg.%. After remaining symptom-free for several months, he neglected to take the probenecid regularly, and soon suffered another bout of leg ache. The serum uric acid level had again become elevated to 6.5 mg.%. After he resumed taking colchicine (6.6

* Received for publication July 21, 1960.
From the Sequoia Hospital, Redwood City, California.
† Supported by a grant from Merck, Sharp & Dohme, West Point, Pa.
Requests for reprints should be addressed to Herman Pepper, M.D., 50 Edgewood Road. Redwood City, California.

mg.) and probenecid, he experienced complete remission of symptoms and seven days later the serum uric acid level was 4.3 mg.%. He has remained symptom-free for the last eight months.

Case 2. A 57-year-old housewife who complained of recurring attacks of leg pain had been treated by several physicians during the last eight years. Her complaints were ascribed to extreme obesity (220 lbs., 5′ 0″ tall). She subsequently lost 40 lbs. when placed on a strict diet and felt better. However, she continued to have leg pain. The attacks usually lasted from two to three weeks and gradually subsided. Recently she had developed a bout of pain in both thighs and calves which became so severe after two weeks that she was hospitalized. At this time the pain was more pronounced in the left leg and was aggravated by weight bearing. General physical and neurologic examinations gave normal findings. X-ray studies of the spine and pelvis were normal. The serum uric acid level was 6.2 mg.%. The patient was treated with colchicine (total dose, 7.2 mg.) followed by probenecid (Benemid, 1 gm. daily), with pronounced improvement. She left the hospital six days later without complaints. The serum uric acid level was then 5 mg.%. She has been maintained without symptoms for 10 months on probenecid therapy.

Case 3. A 53-year-old housewife had had recurrent attacks of leg ache for eight years. She was treated previously and unsuccessfully for myositis and neuritis. The leg ache was described as a persistent, dull discomfort in both thighs and calves, aggravated by walking and standing. The attacks usually lasted from two to three weeks and gradually subsided. The patient was seen during a recurrent bout of leg ache. There was no family history of gout. No tophi were present. The serum uric acid level was 6.3 mg.%. Physical examination revealed no significant findings except for sensitivity to pressure over both calf and thigh muscles. No evidence of disease of the joints was noted. She was given colchicine (total dose, 7.8 mg.), and within three days her leg ache had disappeared and she was able to walk without difficulty. Subsequently she was maintained on probenecid (Benemid, 1 gm. daily) and has remained asymptomatic. The serum uric acid level after 12 days of treatment was 3.3 mg.%.

Case 4. A 60-year-old obese man had had recurrent bouts of leg ache for eight to 10 years. He had been treated previously for myositis and neuritis attributed to standing all day in his work as a bartender. The leg ache was improved considerably by rest. The attacks of leg ache lasted for periods of from two to three weeks, then gradually subsided, but never disappeared completely. When first seen, the patient was in acute cardiac failure. He was placed on digitalis and hydrochlorothiazide (100 mg. daily). Forty-eight hours after medication was begun, he developed severe aches and pains in both legs which were similar to, but more severe, than those he had experienced previously. The serum uric acid level was 7.5 mg.%. After three days of therapy with colchicine (total dose, 10 mg.), he was greatly improved, and stated that for the first time in many years he was free of leg ache. The patient has been maintained without recurrence of symptoms on probenecid (Benemid, 1 gm. daily). Ten days following the attack of leg ache, his serum uric acid level was 5 mg.%.

Case 5. A 70-year-old housewife with a history of hypertensive cardiovascular disease of eight years' duration was seen for a routine physical examination. She had been previously treated with rauwolfia preparations for hypertension, but had received no medication recently. The patient had no complaints except for persistent dull pain in both calves and thighs, which made walking and standing difficult. She had suffered from this periodic leg ache for six years, had received little relief from previously prescribed medication, and was even reluctant to discuss her discomfort. A physical examination revealed moderate obesity and evidence of hypertensive cardiovascular disease without decompensation. The blood pressure was 180/100 mm. Hg. The serum uric acid level was 8.3 mg.%. The patient was given col-

chicine (total dose, 9 gm.), reserpine (0.1 mg.), and hydrochlorothiazide (100 mg. daily). Within four days the leg ache had disappeared. Probenecid (Benemid, 1 gm. daily) was substituted for colchicine and 10 days later the serum uric acid was 3.5 mg.%. The patient has been free of symptoms for eight months while receiving probenecid.

Case 6. A 28-year-old carpenter was seen for a routine physical examination. His complaints included fatigue, heaviness, and aching in both legs, aggravated by standing and relieved by rest. On examination, no pathologic findings were noted, except for tenderness elicited on deep pressure over both calf and thigh muscles. The patient was first treated with analgesics for one week without results. A serum uric acid level was then obtained and found to be 7.7 mg.%. The patient was given colchicine (total dose, 6 mg.) with complete relief of symptoms. He was then placed on probenecid (Benemid, 1 gm. daily). Twelve days later his serum uric acid level was 5 mg.%. He has had no return of symptoms in the past seven months.

Case 7. A 44-year-old teamster had had two attacks of leg pain during a six months' period, each lasting approximately three weeks. The leg pain was persistent, dull, and localized equally in both calf and thigh muscles. Aspirin gave little relief. The patient was in good physical condition. Pronounced sensitivity was elicited by pressure over the leg muscles. A family history of gout was denied. No tophi were present. The serum uric acid level was 8 mg.%. Colcichine (total dose, 7.2 mg.) brought complete relief from the leg pains within 72 hours. Probenecid (Benemid, 1 gm. daily) was then administered with a resultant drop in the serum uric acid level to 4.75 mg.% in 13 days. There has been no recurrence of symptoms in the last five months.

Case 8. A 52-year-old asthenic male was seen because of a minor laceration. He mentioned that he had had periodic attacks of aches and pains in both calf and thigh muscles for the last few years. These symptoms were aggravated by walking and standing, and improved by rest. He disclaimed any other illnesses. Physical examination was negative. Tophi were absent. A family history of gout was denied. The serum uric acid level was 7.1 mg.%. The patient was treated with colchicine, (6.6 mg.) with prompt disappearance of his leg ache. Following 10 days of probenecid (Benemid, 1 gm. daily) his serum uric acid level decreased to 3.9 mg.%. He has remained free of symptoms for two months.

Case 9. A 40-year-old nurse had had recurrent attacks of leg pain for about two years. Every few months she developed dull and persistent pain in both thighs and calves which was aggravated by walking and standing and only partially relieved by rest. The attacks lasted a few weeks and subsided gradually. Physical examination revealed no significant findings except for pedes plani and tenderness of both thigh and calf muscles. The serum uric acid level was normal at 5.7 mg.%. A diagnosis of myositis was made. Corrective shoes brought no relief and analgesics were prescribed, but even large doses provided only partial improvement. The pains gradually subsided a few weeks later. Within five months the patient developed similar symptoms and the serum uric acid levels on two determinations were found to be 5.6 and 5.8 mg.%. Physical therapy and analgesics afforded little relief. When this patient was seen six months later during a particularly severe attack, the serum uric acid levels were again found to be normal. Colchicine (6.6 mg.) was administered and with the onset of diarrhea, the leg pains began to subside and 24 hours later were absent. Probenecid (1 gm. daily) was substituted for colchicine and the patient remained asymptomatic for four months. She then reduced her daily medication to 0.5 gm. and finally discontinued it. Within four weeks she again developed leg ache, although of a milder degree. A short course of colchicine (4.8 gm.) gave relief from her symptoms and the patient has remained well, while taking probenecid (1 gm. daily), for the last six months.

Comment

Eight of the nine patients reported above had suffered from recurrent leg pains for several years. They had been previously treated for myositis or peripheral neuritis by other physicians or by one of us without improvement. Only case 7 had leg ache for six months. Although most of the patients had concurrent disease processes, such as cardiac or gastroenteric disturbances, none of these illnesses was apparently related to the leg ache. Eight patients showed elevated levels of serum uric acid ranging from 6.2 mg.% to 8.3 mg.% (mean, 7.3 mg.%) before treatment was started, and levels between 2.9 mg.% and 5.5 mg.% (mean, 4 mg.%) following treatment. One patient had normal serum uric acid levels at all times. All patients had complete relief from their leg ache for the first time after colchicine-probenecid therapy.

It is important to note that two patients suffered relapses soon after discontinuing their medication. When leg ache recurred in case 1, the serum uric acid had become elevated to 6.5 mg.% and only returned to 4.3 mg.% after resumption of medication. Complete relief of symptoms then followed. The second patient (case 9), who showed normal serum uric acid levels persistently, also had a complete remission of symptoms following resumption of the therapy.

Each patient in this study presented a similar clinical picture, characterized by: (1) a history of recurrent, self-limited attacks of leg ache of varying severity, distributed diffusely over calf and thigh muscles; (2) no family history of gout; (3) absence of tophi; and (4) no evidence of involvement of joints. Eight of the nine patients had elevated levels of serum uric acid, and all improved dramatically following administration of colchicine. Each patient remained free of symptoms while receiving continuous therapy of probenecid (Benemid, 1 gm. daily). Serum uric acid levels returned to, and remained, normal. When specific therapy was discontinued the symptoms returned, and the serum uric acid levels rose to former values. While it is recognized that probenecid will lower the serum uric acid level in asymptomatic hyperuricemia, its discontinuance in our cases brought about recurrence of symptoms.

The psychotherapeutic effect which could have influenced some patients in reporting improvement of their symptoms was minimized by the fact that some of these patients had been treated previously by one of us without success, and no special emphasis was placed on the efficacy of colchicine therapy.

Irregular gout affects women in the majority of cases, but in this study five out of nine patients were men.

The diagnosis of gout is often not made in the absence of the familiar classical picture. Only an awareness that unexplained joint disease may be a disguised attack of gout will suggest the correct diagnosis. Unexplained bouts of leg ache, especially when unrelated to trauma, may well be a manifestation of gout. The term "leg ache" is generally understood to

describe varying degrees of discomfort, aches, and pains in the thigh and calf, regardless of which tissue or structure may be involved by disease. Leg ache may be a symptom in many systemic diseases such as influenza, lead or arsenic poisoning, dengue or Malta fever, trichinosis, myasthenia gravis, progressive muscular dystrophy, peripheral neuritis, or Raynaud's disease. Or it may simply reflect certain bone or joint impairments.

Patients considered to have "leg ache" in this study were limited to those complaining of myalgia of unknown origin. Leg ache occurred as an isolated symptom or was coincidental with other diseases. The constant aches and pains were only relieved by long and absolute rest, and recurred shortly after the slightest exercise was resumed. The only outstanding findings were a varying degree of tenderness elicited on superficial or deep pressure over the calf and thigh muscles. Tenderness of the sciatic nerves was absent. Circulation in both the deep and superficial arterial and venous beds was unimpaired. Once the existence of myalgia was established, the possibility of irregular gout was considered, even in the absence of family history, joint involvement, or tophi. The serum uric acid level was determined in each case, and when found to be elevated, the existence of gout was suspected. The patients were then given colchicine, and only when they responded favorably was the diagnosis of irregular gout established. However, even in the presence of normal levels of serum uric acid, the occurrence of an unexplained attack of leg ache may be due to irregular gout, since an acute attack of gout is not necessarily associated with hyperuricemia. This occurred in case 9, a patient who was seen during two attacks of leg pain, but in whom, because of persistent serum uric acid levels in the normal range, a correct diagnosis was missed. Only when colchicine was given during a third attack and resulted in striking improvement was gout recognized.

Levels of serum uric acid undergo cyclic fluctuations every two or three weeks in males,[2] and reach peak elevations premenstrually in females. Therefore, uric acid determinations should be done twice weekly to confirm the diagnosis of gout. In some instances, therapeutic trials with colchicine are indicated and may prove to be diagnostic. Provocative tests with intramuscular crude liver, a high fat or high purine diet, or alcohol may also be considered if the diagnosis is in doubt.

On the other hand, the simultaneous occurrence of leg ache and persistent hyperuricemia does not necessarily indicate a diagnosis of irregular gout, since high serum uric acid levels can exist in diseases of the hemopoietic system,[3, 4] in carcinoma of the stomach,[5] or in renal insufficiency. The leg pain may merely be a symptom of general debility, or a symptom related directly to the specific disease process. However, none of these diseases were observed in the patients in this study.

It has been recognized that diuretics such as hydrochlorothiazide cause elevation of the level of serum uric acid and thereby may provoke an attack

of gout. This reaction occurred in one patient (case 4), who had suffered from recurrent leg ache for eight to 10 years. When given 100 mg. of hydrochlorothiazide for cardiac decompensation, severe leg pain occurred, and the serum uric acid level was found to be 7.5 mg.%. The patient was given colchicine, followed by probenecid, which provided complete relief of symptoms although hydrochlorothiazide medication was continued. The level of serum uric acid when determined subsequently was 5 mg.%.

Case 5 was also treated with hydrochlorothiazide for hypertensive cardiovascular disease. However, since this patient already was complaining of leg ache, a serum uric acid level was determined before the diuretic was administered and was found to be 8.3 mg.%. In order to prevent a further rise of hyperuricemia and thereby possibly provoke an exacerbation of myalgia, the patient was given colchicine followed by probenecid while continuing with hydrochlorothiazide. This therapy resulted in a decrease of the level of serum uric acid to 3.5 mg.% and in prompt relief of the leg pain. Whereas in the first case an attack of irregular gout was provoked by the diuretic, leg ache was relieved by colchicine and the serum uric acid level was decreased by probenecid in the second patient, although hydrochlorothiazide therapy was continued. Warshaw [6] recently advocated the use of diuretics other than hydrochlorothiazide and benzothiadiazine compounds in patients with a history of gout in order to avoid causing attacks of gouty arthritis. In this study, an attack of irregular gout which had been provoked by the diuretic was terminated by colchicine, and already existing myalgia was relieved by the same medication, in spite of continuous hydrochlorothiazide therapy in each case.

Conclusion

Nine patients presenting similar symptoms of recurrent leg ache of long duration were described. None had a family history of gout and none had joint diseases. All but one patient had elevated levels of serum uric acid. A diagnosis of irregular gout was made in each case after the patient responded favorably to colchicine and after normal levels of serum uric acid were demonstrated following administration of probenecid. All nine patients have remained asymptomatic to date on this therapy.

Summario in Interlingua

Gutta typic es un morbo commun, facile a diagnosticar e tractar, durante que le diagnose de gutta irregular o atypic pote devenir difficile. Le presente reporto describe novem patientes—masculos in le majoritate del casos—in qui le sol symptoma esseva myalgia femoral e sural recognoscite in le curso del tempore como manifestationes de gutta irregular. Omne iste patientes habeva suffrite de recurrente dolores de gamba durante periodos de plure menses o annos; illes omnes habeva essite tractate previemente pro myositis o neuritis peripheric. Le tableau clinic in omne le casos esseva characterisate per (1) attaccos recurrente e auto-limitatori de dolores de gamba de varie grados de severitate, distribuite diffusemente in le suras

e musculos femoral que esseva hyperesthetic pro pression profunde, (2) le absentia de un historia familial de gutta, (3) le absentia de tophos, e (4) nulle indicio pro un implication de articulationes.

Octo del novem patientes habeva elevate nivellos seral de acido uric, amontante a inter 6,2 e 8,3 mg%. Omne le patientes esseva tractate primo con breve cursos de colchicina, resultante in le complete e prompte remission del symptomas. Probenecid (Benamid, 1 g per die) esseva alora substituite e causava un reduction del nivellos de acido uric del sero a inter 2,9 e 5,5 mg%. In un patiente, in qui previe attaccos recurrente de dolores de gamba esseva semper associate con normal nivellos seral de acido uric, colchicina produceva un alleviamento complete, ben que in previe occasiones le attaccos non habeva respondite a varie altere medicationes. Quando le probenecid esseva discontinuate, le dolores de gamba recurreva intra pauc septimanas. Illos esseva supprimite de novo per colchicina e subsequentemente per probenecid.

Le diagnose de gutta irregular esseva suggerite per inexplicate dolores de gamba e hyperuricemia, sed illo poteva esser considerate como establite solmente quando colchicina causava le complete remission del symptomas. Tamen, mesmo in le presentia de nivellos normal de acido uric in le sero, le occurrentia de inexplicabile dolores de gamba pote esser causate per gutta irregular, proque attaccos acute de gutta non es necessarimente associate con hyperuricemia.

BIBLIOGRAPHY

1. Duncan, G. G.: Diseases of Metabolism. 4th Ed., page 656. W. B. Saunders Co., Philadelphia, 1959.
2. Mason, R. M.: Some observations on the blood uric acid levels in gout. Proc. Royal Soc. Med. **44**: 289–292 (April) 1951.
3. Tinney, W. S., Polley, H. F., Hall, B. E., Giffin, H. Z.: Polycythemia vera and gout; report of 8 cases. Proc. Mayo Clin. **20**: 49–55 (Feb.) 1945.
4. Riddle, M. C.: The endogenous uric acid metabolism in pernicious anemia. J. Clin. Invest. **8**: 69–88 (Dec.) 1929.
5. Ficarra, B. J.: Hyperuricemia in gastric cancer. Surgery **19**: 223–228 (Feb.) 1946.
6. Warshaw, L. J.: Acute attack of gout precipitated by chlorothiazide-induced diuresis. J. A. M. A. **172**: 802–807 (Feb. 20) 1959.

TRIMETHYLCOLCHICINIC ACID IN THE TREATMENT OF ACUTE GOUT * †

By STANLEY L. WALLACE, M.D., F.A.C.P., *Brooklyn, N. Y.*

COLCHICINE is an effective drug in the treatment of acute gout. It has diagnostic as well as therapeutic value. Nevertheless, gastrointestinal side effects—hyperperistalsis, diarrhea, nausea, and vomiting—occur in almost all patients to whom therapeutically sufficient colchicine has been given. Other much less frequent but more serious toxic manifestations from relatively small doses have been reported, including agranulocytosis and bone marrow depression,[1] loss of hair,[1, 2] neurologic damage,[3] and death.[4]

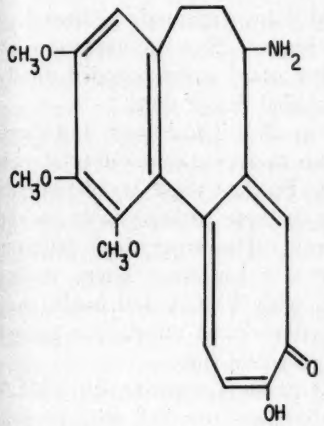
Other colchicine analogs have been introduced in the treatment of acute gout in the hope of separating the therapeutic and toxic effects of colchicine. Desacetylmethylcolchicine was the first colchicine analog to be used in the treatment of gout in this country.[5, 6] It was effective and produced little gastrointestinal toxicity, but had a greater tendency than colchicine to cause agranulocytosis and depilation.[7] Other colchicine analogs have since been screened for their anti-gout activity.[8] Desacetylthiocolchicine was shown to be effective, but its toxic potentialities were great. Colchicoside was less effective than colchicine, and colchiceine was inactive in the treatment of acute gout.

Of all the drugs screened initially, only trimethylcolchicinic acid proved to be both effective and nontoxic. Four of five patients treated with this drug responded well to doses approximately equivalent to those of colchicine.[8] Trimethylcolchicinic acid differs from colchicine in that the acetyl radical from the side chain on the second ring is removed and a hydroxyl group is substituted for the methoxyl group on the side chain on the third ring (Figure 1). The purpose of this paper is to report recent experiences in the treatment of acute gout with trimethylcolchicinic acid (TMCA).

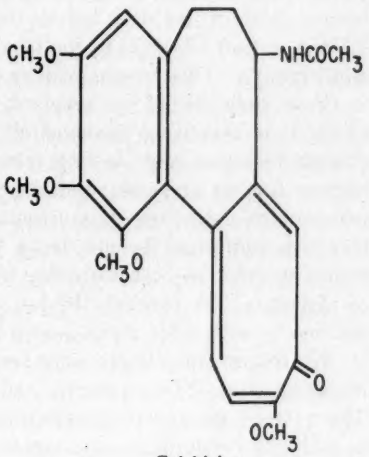
MATERIALS AND METHODS

Thirty-four patients with acute gout were treated with TMCA. All patients demonstrated acute inflammatory arthritis, which was associated in 28 cases with hyperuricemia. Six patients had normal uric acid levels;

* Received for publication July 26, 1960.
Presented in part at the Forty-first Annual Meeting of The American College of Physicians, San Francisco, California, April 7, 1960.
† This work was supported by grants from Roussel, Inc., New York, N. Y., and the New York Chapter of the Arthritis and Rheumatism Foundation. Trimethylcolchicinic acid was supplied by Roussel, Inc. through the courtesy of Dr. A. L. Courtin.
From the Departments of Medicine of State University of New York College of Medicine at New York City, The Jewish Hospital, and Kings County Hospital, Brooklyn, N. Y.
Requests for reprints should be addressed to Stanley L. Wallace, M.D., F.A.C.P., 1122 Ocean Avenue, Brooklyn 30, New York.



Trimethylcolchicinic acid



Colchicine

FIG. 1. Chemical structures.

four of these and three of the other patients were on uricosuric therapy. The remaining two normouricemic patients had had previous attacks of gout which responded to colchicine. Twenty-four other patients had had previous attacks of gout. No patient was included in the group reported here unless the diagnosis of acute gout was unequivocal.

Twenty-nine of the patients were male, five female. Their ages ranged from 38 to 77 years. Eight were Negro, the remainder white. One patient had gout secondary to polycythemia vera; all of the others had primary gout.

TMCA was administered orally in doses of from 5 to 16 mg. Two patients took 8 mg. of TMCA on each of two consecutive days. In all other patients the drug was given as a single total dose; the maximal dose was 10 mg.

The duration of the attack of gout before treatment varied from four hours to three weeks. Most of the patients responding inadequately to TMCA were treated 48 hours later with therapeutic amounts of colchicine. This was done to determine whether these individual episodes of acute gout were susceptible to any colchicine-like drug.

RESULTS

Of the 34 patients treated with TMCA, 26 responded typically, with major or complete clearing of acute gout within 24 to 48 hours. Another four patients responded to TMCA therapy, but partially or incompletely. One female patient in this group had an excellent initial response to TMCA

but on the succeeding day a newly inflamed joint appeared. There had been a delay of five days before therapy was begun. She was treated with TMCA within 12 hours of the onset of her next attack and responded totally and rapidly. This second response is not included in our data.

Four patients did not respond to TMCA at all. These four, and three of the four benefiting inadequately, were given therapeutic amounts of colchicine 48 hours after having taken TMCA. Four of these seven patients had no further response; the attacks of gout in these patients were indeed resistant to colchicine or colchicine-like agents. The other three patients received additional benefit from the course of colchicine. There was a rough correlation between delay in treatment with TMCA and inadequacy of response. In general, the longer the duration of the attack, the poorer the results with TMCA, as is also the case with colchicine.

No major side effects were seen in the 34 patients treated with TMCA for acute gout. Two patients had minimal diarrhea; one had mild nausea. There were no severe gastrointestinal disturbances and no hematologic, neurologic, or dermatologic signs of toxicity.

Seven patients received prophylactic therapy with small daily doses of TMCA. Duration of therapy ranged from one to four months. Three patients received 1 mg. daily, two took 2 mg., and the remaining two 3 mg. each day. None of the patients had episodes of acute gout during the brief period of therapy, but the duration of treatment was too short to evaluate therapeutic effectiveness. None of these patients had any cumulative toxicity. No gastrointestinal, cutaneous, hematologic, or other side effects were seen.

Discussion

The ideal drug in the treatment of gout is one that would completely prevent attacks by altering the metabolic abnormalities of the disease. Short of this, however, a good drug in the therapy of acute gout should have the following characteristics: It should (1) be effective in all or almost all attacks; (2) be effective orally, so that it can be self-administered; (3) work rapidly; (4) be nontoxic, or at the very least should demonstrate a wide margin of safety between the therapeutic and the toxic doses.

No drug presently available fully satisfies all these criteria. TMCA, however, more nearly meets them than does colchicine. TMCA is approximately as effective as colchicine in the treatment of acute gout. Twenty-six of 34 patients in this study responded optimally and four had partial benefit. Persistence of gouty inflammation after colchicine therapy has been estimated to occur in 20%[9] to 25%[10, 11] of patients treated. The doses of TMCA were roughly similar to those of colchicine.

TMCA therapy differs from colchicine chiefly in the freedom of administration its absence of significant toxicity provides. Only minimal and infrequent gastrointestinal side effects occurred during this study. No other

toxicity was seen and there was no cumulative toxicity noted in the patients treated prophylactically.

The drugs differ also in their antimitotic capabilities in experimental systems. TMCA has been shown to have no antimitotic effect against chick fibroblast tissue cultures in concentrations 2,000 to 10,000 times greater than effective levels of colchicine.[12] TMCA produced no antimitotic activity against mouse sarcoma 180 in amounts 1,000 times larger than effective doses of colchicine.[13] Two hundred milligrams per kilogram of body weight of TMCA had no antimitotic effect on regenerating rat liver cells[14] or on mouse corneal epithelium.[15] Evidence of mitotic arrest could be shown in mice bearing sarcoma 37 only with doses of 600 mg./Kg. and 800 mg./Kg.[16] Chronic toxicity studies in rats receiving 2 mg./Kg. daily have shown no evidence of any effect of the drug on cell division.[17]

Antimitotic effects of colchicine in the doses used in the treatment of gout must be extremely rare, although they may occur. Brown and Seed[1] gave colchicine to patients with inoperable carcinoma; one received 12 mg. in four days. Vomiting, diarrhea, and leukopenia occurred. Two other patients were given 21 mg. of colchicine in nine days and 28 mg. in seven days, respectively. Both developed hair loss and leukopenia. Malkinson and Lynfield[2] reported on the use of colchicine therapy in psoriasis; two patients receiving 1.8 to 3 mg. per day developed alopecia in 20 days. Another patient on colchicine and desacetylmethylcolchicine therapy had loss of hair in 16 days. There were no hematologic disturbances, but the hair loss was attributed to cutaneous antimitosis. These doses are similar to those used in the prophylaxis of gout in some patients.

Levine and Silver[18] and Oughterson et al.[19] gave doses of from 1.5 to 2 mg. of colchicine intramuscularly or subcutaneously to humans with cancer. Metaphase arrest occurred in the tumors in 24 hours. Further studies on the cytologic effects of therapeutic amounts of colchicine in human nonneoplastic tissues are indicated.

Desacetylmethylcolchicine and desacetylthiocolchicine, the other colchicine analogs effective in the treatment of gout have, if anything, greater antimitotic potency in humans than does colchicine.[8] Both have been effective in the treatment of leukemia.[20, 21] Neither should be used routinely in the treatment of acute gout because of their marked potential for toxicity.

The doses of TMCA used in this study were arbitrarily chosen to approximate effective doses of colchicine. In view of the lack of clinical toxicity with TMCA, it seems likely that somewhat larger amounts could be used with safety in patients whose initial response is unsatisfactory. Further studies along this line are under way. One would expect TMCA, in addition, to have the same diagnostic specificity as does colchicine in gout, and also to have similar prophylactic effectiveness.

The mechanism whereby TMCA is effective against the inflammation of acute gout is unknown, as is the mode of action of colchicine.[22] The mecha-

nisms are presumably the same. Since TMCA has little gastrointestinal or antimitotic effect, it seems logical to assume, however, that the mechanism of action of colchicine and allied drugs is not related to antimitosis or to gastrointestinal irritation. Previous work[8] has suggested that the tropolone configuration of the side chains on the third ring of the colchicine molecule is necessary for its anti-gout effect. Colchiceine, a derivative of isocolchicine rather than colchicine,[23] with an altered spatial arrangement of these side chains, is ineffective both orally[8] and intravenously.[24] TMCA has the same spatial configuration of the side chains of the third ring as does colchicine, and is similarly effective.

Summary

Trimethylcolchicinic acid, an analog of colchicine, was used in the treatment of 34 patients with acute gout. Twenty-six responded well, and an additional four patients had partial benefit. Four patients did not respond at all.

Mild nausea or diarrhea in three patients were the only side effects noted. No hematologic, cutaneous, or other signs of toxicity were seen.

Seven patients received short term, small dose prophylactic therapy with TMCA. No cumulative toxicity was seen.

Summario in Interlingua

Acido trimethylcolchicinic, un analogo de colchicina, esseva usate in le tractamento de 34 patientes con gutta acute. Vinti-sex respondeva ben; quatro alteres obteneva un beneficio partial. Quatro patientes non respondeva del toto.

Leve grados de nausea o diarrhea in tres casos esseva le sol effectos contrari notate. Nulle signos hematologic, cutanee, o altere con signification de toxicitate esseva constatate.

Le mentionate 34 patientes recipeva le droga in doses unic, con le exception de duo casos in que duo doses esseva usate con un intervallo de 24 horas. Septe altere patientes recipeva cursos de micre doses diurne de acido trimethylcolchicinic como therapia prophylactic durante periodos de inter un e quatro menses. Nulle toxicitate cumulative esseva notate.

BIBLIOGRAPHY

1. Brown, W. O., Seed, L.: Effect of colchicine on human tissues. Amer. J. Clin. Path. **15**: 189, 1945.
2. Malkinson, F. D., Lynfield, Y. L.: Colchicine alopecia. J. Invest. Dermat. **33**: 371, 1959.
3. Layani, F., Aschkenasy, A., Mouzon, M.: Intoxication aigue par la colchicine; important alterations de la leucopoiese. Bull. Mem. Soc. Hôp. Paris **63**: 10, 1947.
4. McLeod, J. G., Phillips, L.: Hypersensitivity to colchicine. Ann. Rheum. Dis. **6**: 224, 1947.
5. Colsky, J., Wallace, S. L., Banowitch, M.: Desacetylmethylcolchicine in acute gouty arthritis. New Engl. J. Med. **253**: 730, 1955.
6. Kuzell, W. C., Schaffarzick, R. W., Naugler, W. E.: Effect of intravenous demecolcine (Colcemid) on acute gout. Arch. Intern. Med. **93**: 153, 1955.

7. Colsky, J., Wallace, S. L., Banowitch, M.: Treatment of acute gouty arthritis with demecolcine. Arch. Intern. Med. **100**: 765, 1957.
8. Wallace, S. L.: Colchicine analogs in the treatment of acute gout. Arthritis Rheum. **2**: 389, 1959.
9. Kuzell, W. C., Schaffarzick, R. W., Naugler, W. E., Koets, P., Mankle, E. A., Brown, B., Champlin, B.: Some observations on 520 gouty patients. J. Chron. Dis. **2**: 645, 1955.
10. Gutman, A. B., Yu, T. F.: Current principles of management in gout. Amer. J. Med. **13**: 744, 1952.
11. de Seze, S., Ryckewaert, A., Levernieux, J., Marteau, R.: Physiopathology, clinical manifestations, and treatment of gout. 2. Clinical and therapeutic studies. Ann. Rheum. Dis. **17**: 15, 1958.
12. Lettre, H., Fernholz, H.: Beitrag zur Beziehung zwischen der Mitosegiftwirkung und der Konstitution von Colchicinderivaten. Ztschr. physiol. Chem. **278**: 175, 1943.
13. Goldberg, B., Ortega, L. G., Goldin, A., Schoenbach, E. B.: Studies on colchicine derivatives. I. Toxicity in mice and effects on mouse sarcoma 180. Cancer **3**: 124, 1950.
14. Brues, A. M., Cohen, A.: Effects of colchicine and related substances on cell division. Biochem. J. **30**: 1363, 1936.
15. Fleischman, W., Ullyot, G. E.: Studies on colchicine derivatives. II. Effect on mitotic activity of the corneal epithelium. Cancer **3**: 130, 1950.
16. Leiter, J., Downing, V., Hartwell, J. L., Shear, M. J.: Damage induced in sarcoma 37 with chemical agents. III. Colchicine derivatives related to trimethylcolchicinic acid and to colchinol. J. Nat. Cancer Inst. **13**: 379, 1952.
17. Courtin, A. L.: Personal communication.
18. Levine, M., Silver, G.: Mitotic response to colchicine in human cancer. Proc. Soc. Exp. Biol. Med. **65**: 54, 1947.
19. Oughterson, A. W., Tennant, R., Hirschfeld, J. W.: Effect of colchicine on human tumors. Proc. Soc. Exp. Biol. Med. **36**: 661, 1937.
20. Leonard, B. J., Wilkerson, J. F.: Desacetylmethylcolchicine in the treatment of myeloid leukemia. Brit. Med. J. **1**: 874, 1955.
21. Burchenal, J. H., Krakoff, I. H.: Newer agents in the treatment of leukemia. Arch. Intern. Med. **98**: 567, 1956.
22. Wallace, S. L.: Colchicine: its clinical pharmacology in acute gout. Amer. J. Med. In press.
23. Horowitz, R. M., Ullyot, G. E.: Colchicine: some reactions of ring C. J. Amer. Chem. Soc. **74**: 587, 1952.
24. Wallace, S. L.: Unpublished data.

CASE REPORTS

ALDOSTERONE-SECRETING ADENOMA: REPORT OF A CASE IN A JUVENILE * †

By MILTON G. CRANE, M.D., JOHN E. HOLLOWAY, M.D., *Los Angeles, California,* and WILLIAM G. WINSOR, M.D., *Whittier, California*

IN 1955 Conn [1] described a new disease syndrome called "primary aldosteronism." Since that time approximately 100 instances of this condition have been observed. Reports of many of these ‡ [2-7, 10] have appeared in the literature. Basically, two types of the syndrome have been recognized. In the adult form, adrenal cortical adenomas have been found to be the cause, whereas in the juvenile form the syndrome has been caused by benign hyperplasia of the adrenal cortex.[8-11]

This is a report of a young woman who was first found to have hypertension at the age of 13 years. The report contains the results of the biochemical defects found when she was studied at the age of 16.

CASE REPORT

This 16-year-old Caucasian female was first found to have hypertension on a routine school physical examination at the age of 13 years. The blood pressure ranged from 150/88 to 190/110 mm. Hg on repeated examinations. In January 1956, the patient complained of headaches, and "passed out" at school. Following this her family physician performed a complete examination, which failed to show any evidence of disease except for a dry skin and a blood pressure of 180/110 mm. of Hg. She was given a trial of various antihypertensive drugs, which included Rauwiloid, Serpasil, and phenobarbital, all without appreciable effect on the hypertension. In September, 1956, she contracted infectious mononucleosis and was in bed for three months. Repeated blood pressure readings during this period of bed-rest were 160/100 mm. Hg or higher.

Because of the continuing hypertension, the patient was seen in consultation by one of us (W. W.) in 1957. At that time she stated that her main difficulties were hypertension and attacks of retro-orbital aching, which usually occurred on hot days. These difficulties had been present for about three years. She denied polyuria, but stated that she had nocturia about two or three times per night, at which time she did pass "a large amount" of urine at each urination. The nocturia was variable, and at times was absent for as long as two to three weeks. She denied any dryness of the

* Received for publication September 14, 1959.

From the Department of Internal Medicine, College of Medical Evangelists, Los Angeles, California, and The Respiratory and Rehabilitation Center for Poliomyelitis, Rancho Los Amigos Hospital, Downey, California.

† This investigation was supported in part by research grant H-2195 from the National Institutes of Health, and by a grant from the Los Angeles County Heart Association.

Requests for reprints should be addressed to Milton G. Crane, M.D., 1720 Brooklyn Avenue, Los Angeles 33, California.

‡ No attempt will be made to include all case reports in the bibliography.

TABLE 1

Initial Studies

Blood Tests	Values
Hemoglobin (gm.%)	13.3–14.1
White Blood Count (per cubic millimeter)	8,600
Serum Sodium (mEq./L.)	146–160
Serum Potassium (mEq./L.)	2.8–3.5
CO_2 Combining Power (mEq./L.)	23–31
Nonprotein Nitrogen (mg.%)	33

Urine Tests	Values
Albumin	Negative 3×
pH	5.0–7.5

throat or any thirst, but tended to drink from 1 to 1.5 L. of liquid daily. Perspiration seemed to occur less freely than is normal. There had been no episodes of muscular paralysis or attacks of muscular weakness. There was only one episode that might be considered to be related to tetany. This occurred as she was having a blood specimen withdrawn. The only other complaint was early morning fatigue. A careful history failed to elicit any suggestion of renal infection or other renal pathology.

The system review was negative except for an occasional bout of palpitation of the heart, some morning anorexia, and a five-pound weight loss over the preceding three months. Menarche was at age 11 years, with normal menstruation since.

TABLE 2

Additional Laboratory Studies

Tests		Results	
Alveolar CO_2	on the	38 and 40 mm. Hg	(Normal, 35–45 mm. Hg)
Arterial pH	same	7.39 and 7.38	(Normal, 7.35–7.45)
CO_2 Content	blood	56.9 and 56.8 Vol. %	(Normal, 45–55)
CO_2 Combining Power	sample	23 and 31 mEq./L.	(Normal, 25–31)
Serum Sodium		150, 160, 152, 146 mEq./L.	
Serum Potassium		3.0, 3.1, 2.8, 3.2 mEq./L.	
Serum Chloride		94, 99, 94, 104 mEq./L.	
Salivary Na/K Ratio			
Unstimulated		0.15 0.10	(Normal, >0.5)
Stimulated		0.43 0.25	(Normal, >1.0)
Extracellular Sodium		2,050 mEq.	
Intracellular Sodium		410 mEq.	
Exchangeable Sodium per Kilogram		49.6 mEq./Kg.	(Normal, 35.1–41.6)
Biologic Decay Time of Na^{22}		21 days	(Normal, 8–14)
Exchangeable Potassium		1,746 mEq.	
Exchangeable Potassium per Kilogram		35.2 mEq./Kg.	(Normal, 38.5–54.4)
Exchangeable "Chloride"		1,550 mEq.	
Exchangeable "Chloride" per Kilogram		31.2 mEq./Kg.	(Normal, 24.9–27.7)
Uropepsin Excretion rate		60 units/hr.	(Normal, 15–40)
Sweat Sodium		14 mEq./L.	(Normal, 47)
Urinary Aldosterone Excretion Rate			
2-18-58		80 μg./24 hrs.	(Normal, 8–12)
2-19-58		70 μg./24 hrs.	(Normal, 8–12)

The past history was essentially noncontributory. The patient had had no operations, injuries, or accidents.

The family history disclosed no familial tendencies toward hypertension, kidney disease, or endocrine defects.

The physical examination revealed that the patient was a well developed, well nourished 16-year-old Caucasian female with a blood pressure of 162/96 mm. of Hg in the right arm and 156/94 mm. of Hg in the left arm. The blood pressure in the leg was 170/100 mm. of Hg. The body build was normal. The skin was free of acne and striae. The heart was normal in size, with a grade II soft systolic murmur limited to the apex. Chvostek's sign was absent. There was no peripheral edema.

Table 1 lists the results of the initial laboratory values. These show that the patient had hypopotassemia.

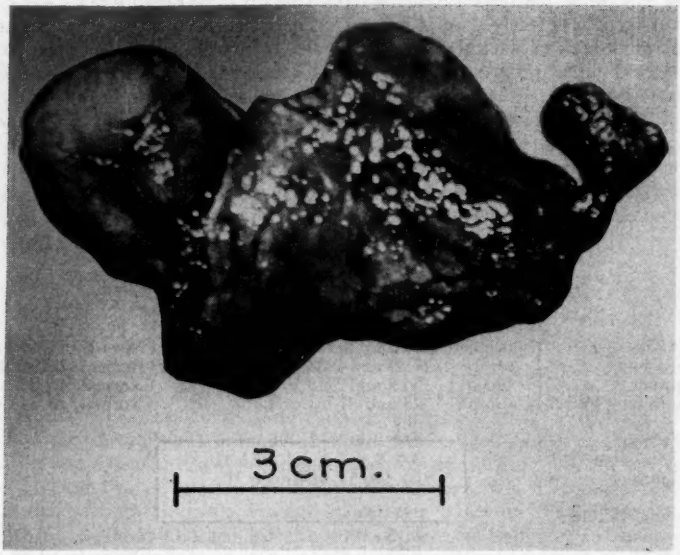


FIG. 1. Gross specimen, showing the adenoma to the upper left hand portion and normal adrenal tissue to the right.

A chest x-ray and an intravenous pyelogram were normal. The blood pressure dropped from 162/100 to 140/70 mm. of Hg with a sodium Amytal test. In view of these preliminary findings, studies were undertaken to determine whether the patient had laboratory evidence of primary aldosteronism. The results of these studies are shown in Table 2.

The patient was next studied to evaluate certain electrolyte and adrenal steroid responses to adrenocorticotropic hormone.

There seemed to be little question that the patient had primary aldosteronism, but we were unable to decide whether an adenoma or hyperplasia of the adrenal cortex was the cause. She was given both adrenocorticotropic hormone and hydrocortisone with 200 mEq. of potassium chloride daily for two days prior to surgery.

On July 18, 1958, the patient was explored surgically for an adrenal cortical tumor by Dr. Frank Rogers. Both adrenal glands, the kidneys and the adjacent areas were examined manually through an anterior abdominal approach. An adrenal

cortical adenoma measuring 2 cm. in diameter was found and removed from its site adjacent to the right adrenal gland (Figure 1). The cut surface demonstrated a thin capsule surrounding a canary yellow homogeneous tumor. The tumor cells were large, with clear cytoplasm, some having a markedly foamy appearance. They were mainly of one histologic type throughout the tumor, and similar in arrangement to the zona fasciculata and glomerulosa (Figure 2). Biopsy of the right adrenal gland showed normal thickness of the three cortical zones. Biopsy of the kidney demonstrated some faintly eosinophilic secretions in the proximal and distal tubules. Certain renal tubular cells of the proximal and distal tubules contained tiny vacuoles, and the free border of many of the cells was broken (Figure 3). These findings in the kidney were consistent with kaliopenic nephropathy.

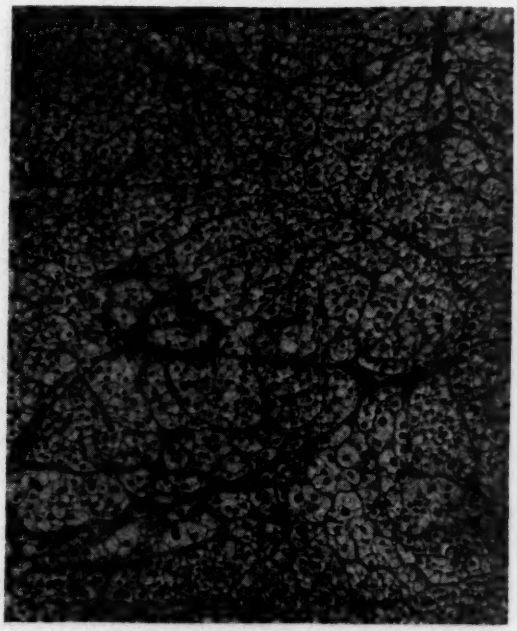


FIG. 2. Photomicrograph of the tumor, demonstrating cellular characteristics. Original magnification × 200.

Following surgery the patient did quite well. The serum potassium was normal on the second day and has remained so since. Potassium supplements were discontinued on the fourth postoperative day. On the fifth day the patient stated that she could sweat easily and that her mouth was no longer dry. The most pleasing thing as far as the patient was concerned was relief from the nocturia, which had ceased on the fifth postoperative day. The blood pressure gradually decreased to within normal limits by the eighth postoperative day, and since then has remained between 116/60 and 138/90 mm. of Hg. The dosage of glucocorticoids and ACTH was gradually decreased, and was discontinued on the twelfth postoperative day. The patient has had no hypertension, nocturia, dry mouth, or retro-orbital headaches since the surgery.

Three months following surgery the patient was again tested for certain electrolyte disturbances. Table 3 gives the results of these studies.

Methods

Sodium and potassium concentrations were determined by Beckman Model DU flame photometer. The arterial pH was determined immediately on the blood electrode of a Beckman Model G pH meter, and the CO_2 content determined by the Van Slyke method. The CO_2 combining power was determined on the same arterial sample (anaerobically obtained) as that used for the measurement of the CO_2 content. Two separate arterial blood samples were tested before operation and two after operation.

The unstimulated saliva was collected in a fasting state without chewing, and the stimulated saliva was collected following 10 minutes of chewing paraffin.

Fig. 3. Photomicrograph of kidney. Original magnification × 200.

The exchangeable sodium was determined with sodium[22]. One-hour and 24-hour plasma samples were counted in a well-type scintillation counter, after which the sodium[23] concentration of the sample was determined by the flame photometer. The one-hour sample was taken as the extracellular content.* The exchangeable sodium was calculated from the 24-hour plasma specimen, corrected for the amount lost in the urine. The biologic decay of sodium was determined from the plasma sodium-22 counting rates of samples obtained from three- to four-day intervals, correcting for any change in plasma sodium concentration.[12]

The exchangeable potassium was determined with potassium[42], using the

* It is realized, of course, that this does not represent the true value, but merely a partition gradient.

specific activity of a one-hour urine sample collected at the end of the 24-hour exchange period, and correcting for the amount lost in the urine. The exchangeable "chloride" was determined by using bromide[82] and the concentration of chloride in the serum.

A thermal sweat specimen was collected with the patient in an atmosphere of 95 to 100° F. and 90% humidity.

The urinary aldosterone excretion rate was determined on two consecutive 24-hour urine samples, using a modification of the Neher-Wettstein method.[13] The method of Reddy[14] was used for the determination of the 17-hydroxy-

TABLE 3

Laboratory Findings Three Months Postoperatively

Tests		Results
Alveolar CO_2	on the	37 and 37 mm. Hg
Arterial pH	same	7.42 and 7.42
CO_2 Content	blood	48.4 and 48.1 Vol. %
CO_2 Combining Power	samples	23 mEq./L.
Serum Sodium		138 and 142 mEq./L.
Serum Potassium		4.5 and 5.2 mEq./L.
Serum Chloride		108 mEq./L.
Salivary Na/K Ratio		
Unstimulated		0.24 0.31
Stimulated		1.10 0.93
Extracellular Sodium		1,691 mEq.
Intracellular Sodium		434 mEq.
Exchangeable Sodium		2,043 mEq.
Exchangeable Sodium/Kg.		42.0 mEq./Kg.
Biologic Decay Time of Na^{22}		15.5 days
Exchangeable Potassium		2,291 mEq.
Exchangeable Potassium/Kg.		47.5 mEq./Kg.
Exchangeable "Chloride"		1,653 mEq.
Exchangeable "Chloride"/Kg.		33.9 mEq./Kg.
Uropepsin Excretion Rate		36 units/hr.
Sweat Sodium		32 mEq./L.
18-hour Urine Concentration S.G.		1.028

steroids; the 17-ketogenic steroids were determined by the method of Norymberski,[15] and the 17-ketosteroids were determined by the method of Drekter.[16]

Urinary uropepsin excretion rates were determined on timed specimens collected under similar conditions as to time of day and relation to meals, and analyzed as described by West.[17]

RESULTS

The initial studies are summarized in Table 1.

Additional Laboratory Findings: The alveolar CO_2, arterial pH, and CO_2 combining power were all within normal limits. The CO_2 content was slightly increased, this being the only evidence of a tendency toward metabolic alkalosis. The elevated exchangeable sodium, the prolonged biologic decay time of sodium,

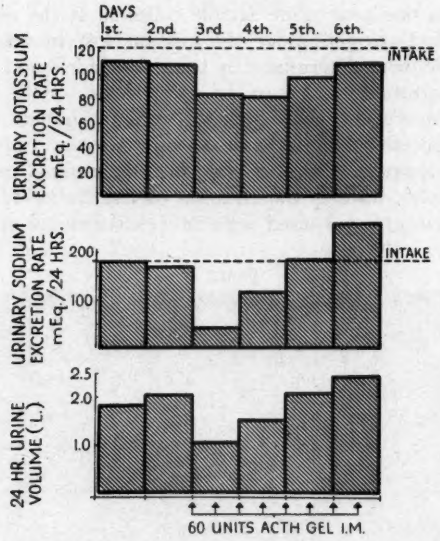


FIG. 4. Influence on urine output, sodium excretion and potassium excretion of adrenocorticotropin (gel), 60 units twice daily.

the lower thermal sweat sodium concentration, and the lower salivary sodium:potassium ratio indicated sodium retention. The low exchangeable potassium indicated a deficit of body potassium. The uropepsin excretion rate was increased, and the urinary aldosterone excretion rate was markedly increased above normal.

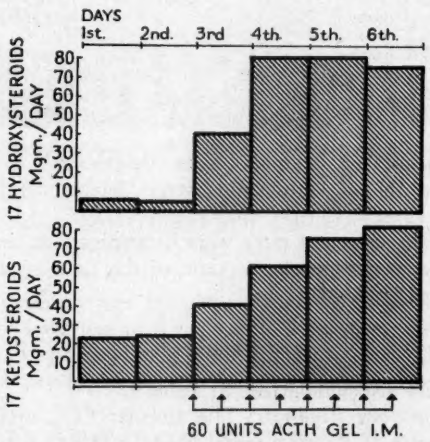


FIG. 5. Influence on 24-hour output of 17-ketosteroids and 17-hydroxysteroids of adrenocorticotropin (gel), 60 units twice daily.

Figure 4 shows that administration of ACTH resulted in a mild diuresis of sodium and a mild retention of potassium. Figure 5 shows that the adrenals under base line conditions were excreting normal quantities of 17-hydroxysteroids and 17-ketosteroids, and that there was a normal response in excretion rate of these steroids with stimulation of adrenocorticotropin.

Van Buchem et al.[8] reported that preoperatively their patient had no free hydrochloric acid in his gastric juice following histamine stimulation. After operation he had a very high hydrochloric acid secretion. The following is a table of the preoperative and postoperative free hydrochloric acid and total degrees of acidity before and following 0.25 mg. of histamine.

	Preoperative		Postoperative	
	Free Acid	Total Acid	Free Acid	Total Acid
Fasting	0	6	10	28
15 minutes	2	38	49	60
30 minutes	16	44	66	75
45 minutes	Patient refused to continue		55	65
60 minutes			34	47

Table 3 gives the values of the electrolyte and other studies three months after removal of the adenoma. The CO_2 combining power, serum sodium, serum potassium, arterial pH, and CO_2 content are all within normal limits. The slight increase in blood buffer found before surgery is no longer present. The salivary sodium : potassium ratios are now in the normal range. The extracellular sodium decreased from 2,050 to 1,691 mEq., and the intracellular sodium decreased from 410 to 352 mEq., resulting in a total decrease in exchangeable sodium of 417 mEq. The exchangeable potassium showed an increase of 545 mEq. (Body weight was essentially the same for the preoperative and the postoperative determinations.) The biologic decay time of sodium was 15 days. The thermal sweat sodium was still slightly below normal. The uropepsin excretion rate is now normal. The 18-hour concentration test was normal.

Through the courtesy of Dr. L. H. Louis, we have the following steroid analyses of the tumor and of the adjacent adrenal gland.

	Non-Tumor Adrenal Cortex (gamma/Kg. of wet tissue)	Tumor Tissue
Aldosterone	84	1139
Hydrocortisone	6528	1898
Corticosterone	2333	2848
Cortisone	55	Undetectable

Discussion

More causes of "essential hypertension" that are surgically correctable are gradually being found. Among these causes are: unilateral ischemic (Goldblatt) kidney, pheochromocytoma, coarctation of the aorta, Cushing's syndrome, congenital adrenal hyperplasia, and primary aldosteronism.

The disease entity named "primary aldosteronism" by Conn is most commonly caused by a benign adrenal cortical adenoma. The clinical features of

this syndrome usually consist of intermittent tetany, paresthesias, headaches, periodic muscular weakness and paralysis, polyuria, polydipsia, and hypertension. The laboratory findings are usually characterized by hypopotassemia, hypernatremia, alkalosis, excessive excretion of sodium-retaining corticoids, and a defect in water reabsorption. The excretion of 17-hydroxysteroids is normal in this condition.

Since the original description by Conn, it now appears that the syndrome may be caused by three types of adrenal cortical lesions. First, unilateral or bilateral hyperplasia of the adrenal cortex has been the cause of the syndrome in four cases.[8-11] So far, all of those with hyperplasia have been below the age of 20. Second, in the majority of cases with this syndrome the cause of the high aldosterone has been found to be benign adrenal cortical adenomas.[1-7, 10] Adenomas are found in the middle age group. Third, the older age group with these clinical manifestations have had adrenal cortical carcinomas. In some instances, aldosterone has not been implicated as the cause. Foye[18] has reported a patient with adrenal cortical carcinoma which produced only mineralocorticoid effect. His patient was temporarily relieved by the removal of the carcinoma. Spaulding[19] has reported a patient with hypocalcemia, hypochloremia, and metabolic alkalosis, apparently caused by an oat-cell type of bronchogenic carcinoma with metastasis to the adrenal gland, which was secreting predominantly mineralocorticoid-like substance, apparently different from aldosterone. Brooks et al.[20] reported a patient with adrenal carcinoma which was secreting abnormally high quantities of aldosterone and another hormone, wildegosterone, related in some way to aldosterone.

The symptomatology in the patient presented here differs very little from that of the usual patient with essential hypertension. She had had no spells of paralysis and no headaches. She seemed to perspire a little less freely than normal and tended to drink a little more water than was usual; however, these symptoms could well have been missed even with a careful history. The nocturia could well have been considered to be secondary to hypertension. This case emphasizes the point that primary aldosteronism should be considered in every patient who has hypertension.

The laboratory studies in this patient bring out some interesting points. The serum potassium was consistently low, but there was very little evidence of metabolic alkalosis. The only evidence of a tendency toward metabolic alkalosis was a slight increase in the CO_2 content. The CO_2 combining power determined on the same sample as CO_2 content was within normal limits. It should be remembered that the procedure for determining CO_2 combining power has certain inherent defects limiting its accuracy. Failure to demonstrate a metabolic alkalosis does not rule out primary aldosteronism. This has been demonstrated in this case as well as in other cases.[2, 4, 5, 7]

Under the influence of aldosterone, the body cells tend to retain sodium, and to excrete potassium in exchange. This results in a decreased thermal sweat sodium, a decreased salivary sodium : potassium ratio, and a higher renal threshold for sodium.

As a result of the aldosterone effect on the body cells, there is an increased exchangeable sodium and a lower exchangeable potassium. Metabolic studies in some other cases[2, 3] seem to indicate that there is also a total body deficit of chloride. This was not demonstrated in this case using radioactive bromide.

Serum values of sodium may be normal or elevated, but serum values do not necessarily reflect a total body deficit or excess. The exchangeable sodium decreased by 417 mEq. and the exchangeable potassium increased by 545 mEq. as a result of the removal of the adenoma in this patient.

The exchangeable chloride as measured with radioactive bromide cannot be assumed to measure the chloride in the body; however, we feel that it does give a fairly close approximation to the extracellular volume. The estimated exchangeable sodium and potassium are usually predicted in reference to the patient's body weight. Fatty tissue, however, has a much lower proportional exchangeable sodium and potassium than do the lean body tissues. Perhaps the exchangeable chloride can be used to determine the lean body mass of an individual for a more nearly accurate estimation of the ideal weight to be used for predicting the patient's normal exchangeable sodium and potassium.

So far, the ratio of the milliequivalents of exchangeable sodium to exchangeable potassium has been a definite aid to us in the diagnosis of primary aldosteronism. We have found in three patients that the preoperative ratios were 1.46, 1.42, and 1.55, whereas the postoperative ratios were 1.11, 0.89, and 1.08 in the same patients. Edematous states, however, would show an increased ratio, and a case of primary aldosteronism with edema would need to be diagnosed by other means.

The salivary sodium : potassium ratios have been a fairly good screening test for primary aldosteronism in our experience. However, we have found that normal values vary from laboratory to laboratory, and may be as low as those found in patients with primary aldosteronism.

We have shown that uropepsin excretion rate is increased in patients with primary aldosteronism.[6, 7] Uropepsin originates in the chief cells of the gastric mucosa. Approximately 1% of the pepsinogen from these cells is absorbed into the circulation and is excreted in the urine. The uropepsin excretion rate has not been found to be consistently increased at all times in the cases we have studied.

Aldosterone secretion, as measured, has not been found to be consistently high in primary aldosteronism. In some patients the aldosterone excretion rate has been found to be normal.[2, 7] The likelihood of cyclic secretory activity of an aldosterone-producing tumor might explain the finding of a varying uropepsin excretion rate.

Primary aldosteronism cannot be diagnosed solely from an increased excretion rate of aldosterone. Fully comparable or even greater increases can occur in various conditions, particularly in "essential" hypertension.[21]

The excretion rates of 17-ketosteroids, 17-hydroxysteroids, and 17-ketogenic steroids have been within normal limits, and no changes in body characteristics suggesting Cushing's syndrome have been present in these cases. The adrenal glands in this condition seem to respond normally to pituitary stimulation, as evidenced by the increased output of 17-ketogenic steroids, 17-hydroxysteroids, and 17-ketosteroids when ACTH was given.

Van Buchem et al.[8] reported that their patient had no free hydrochloric acid in his gastric juice with histamine stimulation before surgery for bilateral hyperplasia of the adrenal cortex. The exact cause for this situation is not known. Results in our case are consistent with a decreased response of gastric mucosa to histamine. It is unfortunate, however, that the patient was uncoöperative at

this critical point and refused a repeat test until after surgery. In a subsequent case (to be reported) we have found that the fasting free hydrochloric acid was normal, and there was dramatic increase in hydrochloric acid secretion with histamine stimulation both preoperatively and postoperatively.

Adenomas in this condition may be quite small. Our first case [6] had an adenoma only 1 cm. in diameter. The anterior abdominal surgical approach was selected for exploration in this case so that both adrenal areas could be examined very carefully for adenomas.

We feel that the preoperative preparation with ACTH and potassium chloride aided this patient to go through the surgery and the postsurgical period smoothly. Both large doses of potassium and glucocorticoids with sodium restriction have been found to tend to correct the high total body sodium and low total body potassium.[1, 2] As suggested by Bartter,[10] cortisone administered preoperatively would further aid in locating small intra-adrenal cortical adenomas by shrinking the normal adrenal cortex.

Summary

The history, physical, and laboratory findings are presented of a young white female who was first found to have hypertension on a routine physical examination at 13 years of age. When she was intensively studied at age 16 she was found to have the electrolyte abnormalities of primary aldosteronism. The removal of a benign adrenal cortical adenoma resulted in correction of the electrolyte abnormalities, and a return to normal of the blood pressure and other clinical manifestations.

Summario in Interlingua

In 1954, Conn faceva le prime reporto de un patiente con aldosteronismo primari. Depost ille tempore, approximativemente 120 casos de iste syndrome ha essite observate. Reportos de plures de istos se trova in le litteratura. Fundamentalmente, duo typos del syndrome ha essite recognoscite. In le forma adulte, adenomas ha essite incontrate usque nunc, durante que in juveniles le syndrome ha essite causate per hyperplasia benigne del cortice adrenal.

Le presente reporto concerne un juvene feminina de racia blanc in qui hypertension esseva primo constatate al etate de 13 annos. Quando le patiente esseva studiate al etate de 16 annos, le sequente anormalitates electrolytic esseva notate: Le kalium del sero variava inter 2,7 e 3,5 mEq/L, le natrium del sero inter 146 e 160 mEq/L. Le chloruro seral variava inter 94 e 104 mEq/L. Le potentia combinatori de CO_2 variava inter 23 e 31 mEq/L. In duo separate occasiones, le contento de CO_2 esseva 56,8 e 56,9 vol%, e le pH arterial in le mesme specimens esseva 7,39 e 7,38. Le proportion de natrium a kalium in non-stimulate saliva esseva 0,15 e 0,10 in duo separate occasiones. Post stimulation per mastication de paraffin, illo montava in le prime caso a 0,43 e in le secunde a 0,25. Le excambiabile natrium de 24 horas esseva 19,6 mEq/kg (a comparar con le norma de 35,7 a 41,6). Le excambiabile kalium esseva 35,2 mEq/kg (a comparar con le norma de 38,5 a 54,4). Le excambiabile chloruro esseva 31,2 mEq/kg (norma: 24,9 a 27,7). Le excretion de uropepsina esseva 60 unitates per hora (norma: 15 a 40). Le natrium del sudor esseva 14 mEq/L (norma: plus que 47). In duo specimens le excretion urinari de aldosterona esseva 80 e 70 gamma per die (norma: 8 a 12). Le intervention chirurgic le 18 de julio 1958 resultava in le discoperta de un benigne adenoma adreno-cortical in adjacentia al glandula dextero-adrenal. Post le operation, le patiente progredeva ben, requirente 412 mEq de kalium le prime duo dies. Le anormalitates electrolytic

del sero esseva corrigite intra duo dies post le operation. Le tension del sanguine descendeva a nivellos normal intra octo dies post le operation. Illo ha remanite normal usque al tempore presente. Dece-un septimanas post le operation, le repetition del supra-listate determinationes resultava in valores que esseva omnes intra le limites normal.

BIBLIOGRAPHY

1. Conn, J. W.: Presidential address. II. Primary aldosteronism, a new clinical syndrome. J. Lab. Clin. Med. **45**: 6, 1955.
2. Chalmers, T. M., Fitzgerald, M. G., James, A. H., Scarborough, H.: Conn's syndrome with severe hypertension. Lancet **1**: 127, 1956.
3. Mader, I. J., Iseri, L. T.: Spontaneous hypopotassemia, hypomagnesemia, alkalosis and tetany due to hypersecretion of corticosterone-like mineralocorticoid. Amer. J. Med. **19**: 976, 1955.
4. Skanse, B., Moller, F., Gydell, K., Johansson, S., Wolff, H. B.: Observations on primary aldosteronism. Acta med. Scandinav. **158**: 181, 1957.
5. Alsted, G., Holberg, P.: Potassium-losing nephritis—primary aldosteronism. Acta med. Scandinav. **161**: 487, 1958.
6. Crane, M. G., Vogel, P. J., Richland, K. J.: Observations on a presumptive case of primary aldosteronism. J. Lab. Clin. Med. **48**: 1, 1956.
7. Crane, M. G., Short, G., Peterson, J. E.: Observations on a case of primary aldosteronism. Amer. J. Med. **24**: 313, 1958.
8. van Buchem, F. S. P., Doorenbos, H., Elings, H. S.: Primary aldosteronism due to adrenocortical hyperplasia. Lancet **2**: 335, 1956.
9. Holten, C., Petersen, V. P.: Malignant hypertension with increased secretion of aldosterone and depletion of potassium. Lancet **2**: 918, 1956.
10. Bartter, F. C., Biglieri, E. G.: Primary aldosteronism: clinical staff conference at the National Institutes of Health. Ann. Intern. Med. **48**: 647, 1958.
11. Mellinger, R., Therian, B., Kline, I. T., Ditzler, J., Smith, R., Fine, G.: Primary aldosteronism, Henry Ford Hosp. Med. Bull. **6**: 1, 1958.
12. Threefoot, S., Burch, G., Reaser, P.: The biological decay periods of sodium in normal man, in patients with congestive heart failure, and in patients with the nephrotic syndrome as determined by Na^{22} as the tracer. J. Lab. Clin. Med. **34**: 1, 1949.
13. Neher, R., Wettstein, A.: Physicochemical estimation of aldosterone in urine. J. Clin. Invest. **35**: 800, 1956.
14. Reddy, W. J.: Modification of the Reddy-Jenkins-Thorn method for the estimation of 17-hydroxycorticoids in urine. Metabolism **3**: 489, 1954.
15. Norymberski, J. K., Stubbs, R. D., West, H. F.: Assessment of adreno-cortical activity by assay of 17-ketogenic steroids in urine. Lancet **1**: 1276, 1953.
16. Drekter, I. J., Heisler, A., Scism, G. R., Stern, S., Pearson, S., McGavack, T. H.: The determination of urinary steroids. I. The preparation of pigment-free extracts and a simplified procedure for the estimation of total 17-ketosteroids. J. Clin. Endocr. **12**: 55, 1952.
17. West, P. M., Ellis, F. W., and Scott, B. L.: A simplified method for determining the excretion rate of uropepsin. J. Lab. Clin. Med. **39**: 159, 1952.
18. Foye, L. V., Jr., Feichtmeir, T. V.: Adrenal cortical carcinoma producing solely mineralocorticoid effect. Amer. J. Med. **19**: 966, 1955.
19. Spaulding, W. B., Oille, W. A., Gornall, A. G.: Mineralocorticoid-like disturbance associated with adrenal metastases from a bronchogenic carcinoma. Ann. Intern. Med. **42**: 444, 1955.
20. Brooks, R. V., Mills, I. H., Prunty, F. T. G.: A new urinary steroid related to mineral metabolism. Lancet **2**: 925, 1956.
21. Genest, J., Koiw, E., Nowaczynski, W., Leboeuf, G.: Further studies on urinary aldosterone in human arterial hypertension. Proc. Soc. Exp. Biol. Med. **97**: 676, 1958.

HYPERTENSION SECONDARY TO ANEURYSM OF THE RENAL ARTERY: REPORT OF A CASE OF LONG DURATION CURED BY NEPHRECTOMY *

By RICHARD L. KLEIN, M.D., *St. Louis, Missouri,* and Major JOHN A. MCCHESNEY (MC) USAF, *Travis Air Force Base, California*

SINCE the classic experiments of Goldblatt,[1] interest in the renal origin of hypertension has increased greatly, in part because hypertension occurring in association with unilateral renal disease is potentially curable by removal of the involved organ. Unilateral renal arterial disease, though less commonly associated with hypertension than is unilateral pyelonephritis, has been associated with a much higher rate of cured hypertension following nephrectomy. The general opinion, as reflected by Thompson and Smithwick,[2] is that renal arterial lesions represent the closest clinical counterpart to the experimental Goldblatt kidney.

Characteristically, patients with renal arterial disease have an abrupt onset of hypertension. Flank pain or a history of recent trauma to the kidney is common, and the hypertension frequently runs an accelerated course, with or without progressive deterioration of renal function.

The following case is reported in detail to illustrate the unusual occurrence of hypertension of 13 years' duration associated with unilateral renal artery aneurysm, and apparently cured by nephrectomy.

CASE REPORT †

A 26-year-old housewife was admitted to the Barnes Hospital for the first time on November 7, 1957, for evaluation of high blood pressure of 13 years' duration.

She had been in excellent health during childhood until 1944, when at age 13 she rather suddenly developed severe headaches. These were episodic, lasting as long as three days, were located either diffusely or over the right temporal region, and were accompanied occasionally by nausea and vomiting. The persistence of these symptoms necessitated hospitalization, at which time her systolic blood pressure was found to be 180 mm. Hg. She was treated with an unknown medication, which produced symptomatic relief. In 1951 she was admitted to another hospital for evaluation of hypertension. All tests performed, including phenolsulfonphthalein excretion and ability to concentrate urine, were within the limits of normal. There was no apparent fall in blood pressure following oral administration of Sodium Amytal. Systolic blood pressure varied between 150 and 170 mm. Hg. (There is no documentation of her diastolic blood pressure.) She was treated with hexamethonium and hydralazine hydrochloride. During 1951 and 1952 her blood pressure, determined frequently, was consistently at hypertensive levels. In August, 1954, during her first pregnancy, she was first seen at the Scott Air Force Base Hospital, where she was again noted to be hypertensive (Figure 1). The urine contained

* Received for publication September 28, 1959.

From the Department of Medicine, Washington University School of Medicine, the Barnes Hospital, St. Louis, Missouri, and the Scott Air Force Base Hospital, Illinois.

Requests for reprints should be addressed to Captain Richard L. Klein, (MC), U. S. Army Hospital, Fort Campbell, Ky.

† A brief summary of this case appears in a review by Cordonnier of seven patients with unilateral renal artery disease and hypertension (J. Urol. **82**: 1–9, 1959).

3-plus proteinuria, and occasional white blood cells and casts, type unspecified, were found in the centrifuged sediment. With intravenous pyelography, a slight degree of hydronephrosis was observed on the right, but the roentgenograms were otherwise unremarkable. A Rauwolfia preparation, barbiturates, and veratrum alkaloids were administered, with little benefit. Blood pressure rose to high levels at the time of spontaneous delivery of a normal child at seven and one-half months' gestation. Discharge diagnoses were pre-eclampsia and benign essential hypertension. The patient was again seen at the Scott Air Force Base Hospital in January, 1956, because of pregnancy, which subsequently terminated with the delivery of a seven month stillborn child. During the latter part of this pregnancy her blood pressure rose to levels around 200/100 mm. Hg. She was treated with hydralazine hydrochloride

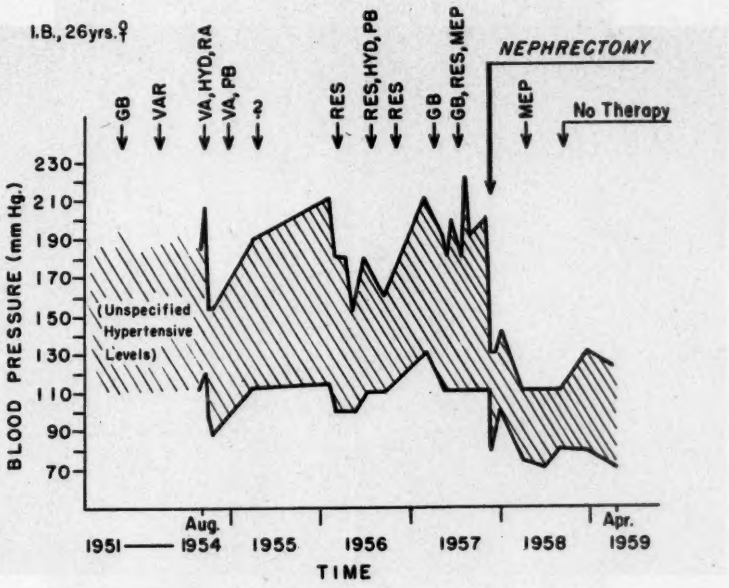


FIG. 1. Effect of various therapeutic agents on the patient's blood pressure. Legend: GB, ganglionic blocking agent; VAR, various antihypertensive medications; VA, veratrum alkaloids; RA, Rauwolfia alkaloids; HYD, hydralazine; PB, phenobarbital; RES, reserpine; MEP, meprobamate.

and reserpine, with good control of hypertension until February, 1957, when the reading of 210/130 mm. Hg prompted the addition of pentolinium tartrate to her therapy. Her blood pressure varied between 180/100 and 190/110 mm. Hg.

Additional studies were made at the Scott Air Force Base Hospital in April, 1957. Her blood pressure was 180/110 mm. Hg. The urine contained 4-plus proteinuria (possibly an analytic error), and 18 to 20 red blood cells per high power field in the centrifuged sediment. The results of an Addis count on a 12-hour urine were 76,000,000 white blood cells, 133,000,000 red blood cells and 44,000,000 epithelial cells. Quantitative protein was 0.02 gm. in 24 hours. With intravenous pyelography (Figure 2) there was slightly decreased concentration of dye by the right kidney, with normal concentration by the left side. Both kidneys appeared to be normal and

comparable with respect to size and shape. Differential renal function studies were performed with catheters placed in both ureters. The left kidney excreted 76 ml. of urine in one hour, while the right kidney excreted 435 ml. A trace of protein was found in the urine from each ureter. Mecamylamine, reserpine, and phenobarbital were administered. In July, 1957, the patient was admitted to the Scott Air Force Base Hospital for aortography. Her blood pressure varied between 190/110 and 222/120 mm. Hg in the sitting position, and was 150/108 mm. Hg standing. Translumbar aortography was performed on August 7, 1957, at which time 30 ml. of 50% Hypaque were injected. The right renal artery and its ramifications appeared to be normal, but the existence of a small aneurysm of the left renal artery was suspected. The patient was discharged in October, 1957, on the same therapeutic regimen. She entered the Barnes Hospital on November 7, 1957, on the service of Dr. James F.

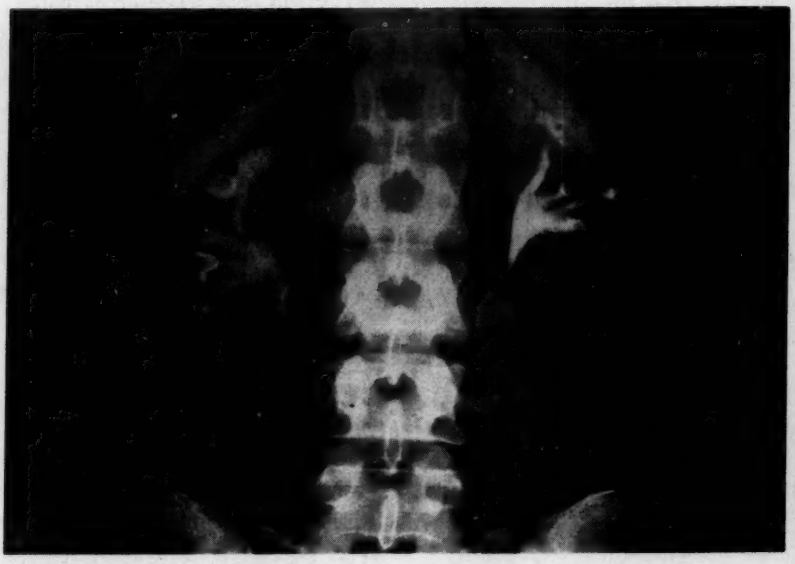


FIG. 2. Intravenous pyelogram performed April, 1957; dye has been concentrated by the right kidney slightly less than by the left kidney.

Nickel, for further evaluation of hypertension. Her interval history was unremarkable except for infrequent headaches. She denied symptoms of congestive heart failure, nocturia, dizziness, nausea, or visual complaints. The family history, past history, and review of systems were noncontributory.

The patient was a young, attractive white female appearing to be neither acutely nor chronically ill. The significant vital signs were: blood pressure in the left arm, 200/110; right arm, 205/112; left leg, 225/120; right leg, 230/125 mm. of Hg; pulse, 80 per minute; respirations, 18 per minute; temperature, 37° C. orally. Slight arteriovenous nicking and arteriolar narrowing and spasm were observed on retinal examination. No hemorrhages or exudates were seen. There were no signs of cardiac decompensation. The point of maximal cardiac impulse was palpated 12 cm. to the left of the midsternal line in the fifth intercostal space. The heart sounds were strong. A grade 2 (6 grades) blowing systolic murmur was heard at the apex,

and the aortic second sound was louder than the pulmonic second sound. No abdominal masses or organs were felt. Peripheral pulses were strong and equal, and the remainder of the examination was not remarkable.

Admission laboratory data, including blood counts, were unremarkable, and the serologic test for syphilis was negative. The results of urinalysis were: specific gravity, 1.018; pH, 6.0; protein, trace; test for reducing substances, negative; white blood cells, five to six, and red blood cells, one to two per high power field in the centrifuged sediment. An electrocardiogram was interpreted as being consistent with left ventricular enlargement on the basis of voltage. Chest roentgenograms demonstrated clear lung fields and a normal cardiac configuration. The blood nonprotein

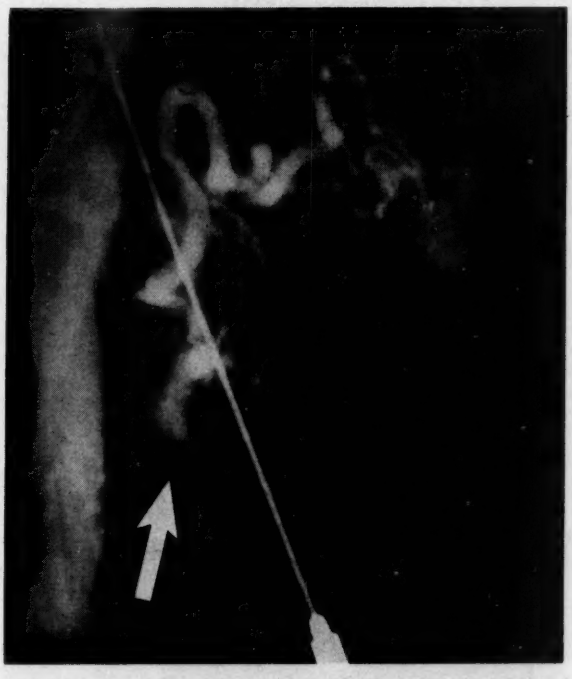


FIG. 3. Translumbar aortogram. An aneurysmal dilatation of the inferior branch of the left renal artery is demonstrated.

nitrogen was 18 mg.%; blood urea nitrogen, 7 mg.%; fasting blood sugar, 74 mg.%; cholesterol, 160 mg.%. Serum proteins were within limits of normal. The administration of 0.6 gm. Sodium Amytal orally failed to reduce diastolic blood pressure below 100 mm. Hg. A phentolamine test was negative. The four-hour endogenous creatinine clearance was 90 ml. per minute; the excretion of phenolsulfonphthalein was 35% in 15 minutes, and 80% in two hours. Three subsequent urinalyses were negative for protein. An aneurysmal dilatation of the inferior branch of the left renal artery was demonstrated by translumbar aortography, performed by Dr. Robert Lund on November 15, 1957, using 50 ml. of 50% Miokon. The remainder of the left renal artery was believed to be decreased in caliber in comparison with the right (Figure 3). No abnormalities were demonstrated by retrograde pyelog-

raphy. Differential studies were performed by Dr. M. Richard Carlin, utilizing bilateral ureteral catheters; the results are shown in Table 1. The left kidney excreted a significantly smaller amount of urine than the right kidney, and the urinary sodium concentration was likewise greater in the right kidney urine. The data were interpreted as showing a reduced glomerular filtration rate per nephron in the left kidney, compatible with extrinsic renal arterial disease.

On November 23, 1957, a left nephrectomy was performed under general anesthesia by Dr. Carlin, without incident. The removed kidney was of normal size, weighed 150 gm., and appeared to be unremarkable to gross inspection. A large

TABLE 1

Results of Differential Renal Function Studies

Time		Right Ureteral Urine	Left Ureteral Urine	Bladder Urine
9:10 a.m.	A. Intravenous infusion of 1,000 ml. of 5% glucose in water			
9:25–9:55 a.m.	Volume in ml.	147	45	100
	Sodium in mEq./L.	47	21	33
	Protein	0	2+	Trace
	Specific gravity	1.008	1.017	—
9:57 a.m.	B. Injection of 1 ml. phenolsulfonphthalein			
	Appearance time in minutes	2	3	3
	Volume in ml. in 15 minutes	80	60	120
	Percentage of administered PSP (15 minutes)	15	5	10
10:15–10:45 a.m.	C. Collection period for sodium and potassium			
	Volume in ml.	150	120	140
	Sodium in mEq./L.	14.8	4.9	13.5
	Potassium in mEq./L.	2.6	2.5	2.0
10:53–11:15 a.m.	D. Intravenous infusion of 100 ml. 5% sodium chloride			
	Volume in ml.	90.0	30.0	65.0
	Sodium in mEq./L.	61.0	15.0	37.5
	Potassium in mEq./L.	6.8	6.6	4.0

Injection of 2 ml. of indigo carmine into each of the ureteral catheters indicated that the major portion of the bladder urine came through the right catheter.

dilatation of the inferior branch of the left renal artery, measuring approximately 1 cm. in each dimension, was observed to begin immediately where the inferior renal artery arose from the main renal artery, and to extend out onto two branches of the inferior renal artery (Figure 4). After fixation, a plaque measuring 2 by 2 mm. was seen in the proximal portion of the main renal artery, almost completely occluding the lumen. Attenuation of the elastic tissue was seen in the walls of the aneurysm, together with disintegration and edema of the muscle. With the exception of minimal arteriolar nephrosclerosis, microscopic examination of the kidney and ureter was within limits of normal. There was minimal intrarenal vascular change.

During operation the patient's vital signs were always stable. Prior to nephrec-

tomy the blood pressure had been 190/140 mm. Hg. Fifteen minutes after removal of the kidney, the blood pressure was 160/110, and 50 minutes later it was 130/80 mm. Hg. The postoperative course was uneventful, with blood pressure varying from 120/70 to 150/90 mm. Hg; no specific antihypertensive medication was given.

In the 18 months since operation the patient has been seen at the Scott Air Force Base Hospital at monthly intervals. Her blood pressure has ranged between 130/90 and 110/70 mm. Hg, except for an isolated determination of 140/100 mm. Hg approximately six weeks after operation. An intravenous pyelogram in August, 1958,

FIG. 4. The surgically removed left kidney. The aneurysmal dilatation of the inferior branch of the left renal artery is seen to begin where this vessel branches off from the main renal artery.

was interpreted as showing a normal right kidney. The patient has felt entirely well, and has required no antihypertensive or ataractic medication. The specific gravity of the urine (in the nonhydropenic state) was 1.019; the reaction for reducing substances and protein was negative; and four to five white blood cells per high power field were seen in the centrifuged sediment. A blood nonprotein nitrogen determination in April, 1959, was 37 mg.% (within the accepted range of normal for this laboratory), and excretion of phenolsulfonphthalein dye was 26% in 15 minutes and 81% in two hours. There was no interval change in the appearance of her ocular fundi.

Discussion

The evaluation of patients with hypertension has grown progressively more complex as new diagnostic procedures have become available. Although relatively infrequent, potentially remediable conditions such as pheochromocytoma, aldosteronoma, coarctation of the aorta, and unilateral renal disease are being discovered with a frequency proportionate to the diagnostic zeal of the physician.

Perera and Heilig have called attention to the clinical characteristics of hypertension caused by unilateral renal arterial disease.[8] Of 20 patients apparently cured of their hypertension by nephrectomy, none gave a history of long-standing hypertension, and severe retinopathy was seen in all except young children and one patient with an extremely brief history of hypertension. These authors emphasized that the process is most often acute in onset, severe in nature, and accelerated in course; they suggested that the presence or absence of this pattern may be of prognostic significance in selecting patients most likely to respond to nephrectomy. Published case reports [3-6] illustrate the frequent history of symptoms of renal insult, whether by external trauma, arterial embolization, thrombosis, or calculi. It seems reasonable, however, that a substantial number of patients may run a benign course, characterized merely by labile or stable hypertension for many years.[6-8] The patient described in the present report is an example of the latter, manifesting sustained hypertension for 13 years, essentially unaffected by antihypertensive agents.* She had infrequent symptoms referable to her hypertension, and was able to withstand two pregnancies. The absence of severe retinopathy and the apparent cure by nephrectomy suggest that diffuse vascular disease in this patient was surprisingly minimal or was, at the least, reversible following removal of the ischemic kidney.

The value of aortography and differential renal function studies in the diagnosis of unilateral renal arterial disease is demonstrated by this case. The presence of an essentially normal intravenous urogram is consistent with the experience of Poutasse and Dustan,[9] who observed that the size and function of the involved kidney were considered to be within normal limits, or similar to the contralateral kidney in 11 of 22 instances of unilateral renal artery disease. The presence of a normal intravenous urogram should therefore not mitigate against the diagnosis of renal artery occlusive disease. Aortography is a procedure which may be of extreme importance diagnostically. When performed by the translumbar route, however, it has been associated with a mortality of 0.8%.[10] The occasional complications of translumbar aortography, including various renal complications, have been extensively reviewed elsewhere.[10, 11] The technic of Seldinger, by which a flexible polyethylene catheter is inserted into the aorta by percutaneous puncture of the femoral artery, would appear to correct most of the disadvantages inherent in the translumbar approach.[12] Most of the complications of the translumbar technic which related to the site of injection are obviated. The quality of films, moreover, is improved, since the patient can be placed in any desired position, and the catheter can be left in place between series of films.

* Since the preparation of this paper, Ullmann et al. (Amer. J. Med. 26: 960–964, 1959) have reported the case of a 12-year-old boy with hypertension of 10 years' duration, related to narrowing of the right renal artery. The diagnosis was established similarly with the use of aortography and separate renal function studies, and nephrectomy was apparently curative.

Differential qualitative and quantitative renal function studies may be of diagnostic significance in demonstrating renal arterial disease in the absence of associated parenchymal disease. Results indicative of a lesion include a variable reduction in water excretion and urinary sodium concentration by the involved kidney as compared with the contralateral normal kidney. These observations are consistent with the experimental findings of Mueller et al.,[13] who noted that in the unanesthetized dog a slight decrease in glomerular filtration rate produced by light constriction of the renal artery caused a great fall in urinary sodium concentration and water excretion. It is significant that the combined glomerular filtration rate of *both* kidneys (as measured by the creatine clearance) was within normal limits in our patient. The diagnosis of unilateral renal arterial disease would therefore have been obscured had differential studies not been performed.

Certain conclusions may be derived from the experiences with this patient: first, a relatively long history of benign hypertensive disease should not necessarily preclude unilateral renal arterial disease; second, although the long duration of nephrogenic hypertension has been generally associated with poor therapeutic results following nephrectomy,[14] hypertension related to certain renal arterial lesions may be present for many years and still be potentially curable by nephrectomy; and third, aortography and differential renal function studies may indicate unilateral renal arterial disease in the face of grossly normal renal function. These procedures appear to have an established place in the evaluation of unilateral renal disease, and their use may be profitably extended to the evaluation of many patients with unexplained hypertension.

Summary

The case of a 26-year-old female is presented to illustrate apparent cure of long-standing hypertension associated with an aneurysm of the left renal artery. It is noteworthy that her hypertension was of 13 years' duration, and that her course was relatively benign. The diagnosis was established preoperatively with the aid of translumbar aortography and differential renal function studies. The patient has been normotensive for 18 months following removal of the affected kidney.

Summario in Interlingua

Es presentate le caso de un feminina de 26 annos de etate pro illustrar le curation apparente de hypertension de longe duration associate con un aneurysmo del arteria sinistro-renal. Es notabile que le hypertension in iste patiente esseva presente depost 13 annos e habeva habite un curso relativemente benigne e essentialmente non-influentiate per agentes antihypertensive. Le diagnose de morbo reno-arterial unilateral esseva establite ante le operation con le adjuta de aortographia translumbar e studios reno-functional differential. Le patiente es normotensive depost 18 menses post le ablation del ren que esseva afficite.

Certe conclusiones pote esser derivate ab le experientias con iste patiente. Primo, un relativemente longe historia de benigne morbo hypertensive non exclude necessarimente morbo reno-arterial unilateral. Secundo, ben que le longe duration de hypertension nephrogenic ha generalmente essite associate con mal resultatos therapeutic post nephrectomia, hypertension relationate a certe lesiones reno-arterial pote esser presente durante multe annos e remaner potentialmente curabile per nephrectomia. Tertio, aortographia e studios differential del functiones renal pote

indicar morbo unilateral de arteria renal in le presentia de functiones renal que es grossiermente normal.

BIBLIOGRAPHY

1. Goldblatt, H.: Studies on experimental hypertension. V. The pathogenesis of experimental hypertension due to renal ischemia. Ann. Intern. Med. **11**: 69, 1937.
2. Thompson, J. E., Smithwick, R. H.: Human hypertension due to unilateral renal disease with special reference to renal artery lesions. Angiology **3**: 493, 1952.
3. Perera, G. A., Heilig, A. W.: Clinical characteristics of hypertension associated with unilateral renal disease. Circulation **6**: 549, 1952.
4. Pastor, B. H., Myerson, R. M., Wohl, G. T., Rouse, P. V.: Hypertension associated with renal artery aneurysm and relieved by nephrectomy. Ann. Intern. Med. **42**: 1122, 1955.
5. Hyman, A., Leiter, H. E.: Essential hypertension associated with unilateral disease of the kidneys. J. Mt. Sinai Hosp. **12**: 335, 1945–46.
6. Howard, J. E., Bertrong, M., Gould, D. M., Yendt, E. R.: Hypertension resulting from unilateral renal vascular disease and its relief by nephrectomy. Bull. Johns Hopkins Hosp. **94**: 51, 1954.
7. Schaffer, A. J., Markowitz, M.: Hypertension treated by nephrectomy: a report of 4 additional cases and re-evaluation of prognosis and criteria for operation. Amer. J. Med. Sci. **227**: 417, 1954.
8. Smith, H. W.: Unilateral nephrectomy in hypertensive disease. J. Urol. **76**: 685, 1956.
9. Poutasse, E. F., Dustan, H. P.: Arteriosclerosis and renal hypertension. Indications for aortography in hypertensive patients and results of surgical treatment of obstructive lesions of renal artery. J. A. M. A. **165**: 1521, 1957.
10. Stokes, J. M., Butcher, H. R., Jr.: Complications of translumbar aortography related to site of injection. Arch. Surg. **75**: 770, 1957.
11. Crawford, E. S., Beall, A. C., Moyer, J. H., DeBakey, M. E.: Complications of aortography. Surg., Gynec., Obstet. **104**: 129, 1957.
12. Seldinger, S. I.: Catheter replacement of the needle in precutaneous arteriography. Acta radiol. **39**: 368, 1953.
13. Mueller, C. B., Surtshin, A., Carlin, M. R., White, H. L.: Glomerular and tubular influences on sodium and water excretion. Amer. J. Physiol. **165**: 411, 1951.
14. Braasch, W. F.: End results following nephrectomy in patients with hypertension. J. Urol. **68**: 6, 1952.

CHOLESTEROL PERICARDITIS *

By R. B. HAINING, M.D., *Glendale, California,* and R. G. HAINING, M.D., *Boston, Massachusetts*

LITTLE or nothing is known of the pathogenesis of cholesterol pericarditis. Including their own case, Moe and Campos [1] found 12 cases reported in the world literature, only four of these in American journals. Of the latter four, two were studied at autopsy. One of the four, reported by Creech and associates,[2] was successfully treated by pericardiectomy.

* Received for publication September 15, 1959.
Requests for reprints should be addressed to R. B. Haining, M.D., 540 North Central, Glendale 3, California.

In March, 1959, Genecin [3] published a remarkable study of chronic pericardial effusion in two brothers, aged 17 and 24. The younger brother had cholesterol pericarditis and was successfully treated by pericardiectomy. The other brother was considered to have "pericardial effusion of unknown etiology." He has remained well for three years following one pericardial tap.

The man whose history is presented here almost certainly had pericardial effusion in 1943, when he was 38. Apparently it was not large enough to cause symptoms except at infrequent intervals. In 1951, when we first saw him, the diagnosis of pericardial effusion was obvious. Several pericardial taps were performed, and the fluid recovered was sterile, creamy in character and in the first three taps had a high content of cholesterol crystals. Pericardiectomy was performed on November 20, 1951. The patient made a good recovery, and has remained well to this date.

Case Report

A 45-year-old white man in 1943, at age 38, had experienced severe pain over the sternum, radiating to the back. The pain was worse on deep breathing, and he sweated profusely. He was examined by a physician within 30 minutes of the onset of pain, was told that he had had a heart attack, and was confined to bed for 24 hours. One week later he was seen in consultation by a second physician, who found that he had enlargement of the heart and hypothyroidism. He was given thyroid, gr. 1 daily, and within a few weeks felt well enough to resume work.

One year later the patient complained of faintness and cold sweating. There was no pain. On study, it was found that the heart size had increased, and a diagnosis of pericardial effusion was made. The examining physician advised a pericardial tap, but this was not done. The patient gradually improved and resumed work as a professional musician (pianist).

He was first seen in our office June 4, 1951. He was 5 feet 6 inches tall and weighed 204 pounds. His main complaint was a sensation of pressure below the xiphoid process and along the left costal margin. He disclaimed pain, but said the sensation of pressure was constant and had been present for "several years." There was moderate distention of the jugular veins in the recumbent position. The liver was palpable three fingerbreadths below the right costal margin; it was smooth and not tender. The spleen could not be palpated. The blood pressure was 140/90 mm. of Hg. The heart rhythm was regular at a rate of 80 per minute. No apical impulse could be felt. The area of cardiac dullness was greatly increased bilaterally. Heart sounds were faint, and no murmurs were heard. An electrocardiogram showed low voltage in all leads. There was no Q wave, no S-T segment deviation, and no T wave inversion. A chest x-ray demonstrated some prominence of the hilar shadows and perihilar markings, though the lung fields were clear bilaterally. The heart shadow was markedly increased, its transverse diameter being about three-fourths the diameter of the chest. The enlargement extended up to the region of the great vessels. Lateral views showed the heart shadow to extend posteriorly beyond the anterior margins of the spine. It completely occluded the space between the heart and the posterior sternal margin.

On June 21 the patient was admitted to the Glendale Sanitarium and Hospital, where two pericardial taps were performed, yielding 300 and 200 ml. of fluid, respectively. Equivalent amounts of air were introduced. The fluid was creamy in appearance and consistency, nonhemorrhagic, sterile on culture, and "loaded" with cholesterol crystals. A chest x-ray on June 24 was interpreted as follows: "This

chest film reveals a markedly enlarged heart shadow which is due to pericardial effusion. Some of the fluid has been removed and air has been injected, and a fluid level is present. The left portion of the pericardial sac outlined on this view does not appear to be thickened. The lung fields appear clear." The pathologist's report (June 26, 1951) on the button made from the pericardial fluid stated that ". . . this is consistent with cholesterol pericarditis."

On September 21, 1951, the patient was hospitalized again, and on the night of admission a pericardial tap yielded 900 ml. of fluid similar in character to the fluid from previous taps. A chest x-ray on September 22 was interpreted as follows: ". . . There is a pneumopericardium with fluid level near the inferior aspect of the pericardial sac. The heart does not appear greatly enlarged, though it may be larger than usual. Comparison with the film of June 22 would seem to indicate no material change." On September 22 the patient's temperature rose to 103° F., but with the administration of penicillin and later of Chloromycetin, he was afebrile within 10 days. Laboratory reports on the pericardial fluid were as follows: *August 17, 1951.* Gram stain: much debris, no organisms seen, moderate pus; acid-fast stain: no acid-fast bacilli seen; culture (guinea pig inoculation): negative for acid-fast bacilli. *October 1, 1951.* Gram stain: much debris, no organisms seen; culture: negative in 48 hours. *November 11, 1951.* Guinea pig (inoculated October 1, 1951, autopsied November 12, 1951): negative for acid-fast bacilli. *October 7, 1951.* Blood culture (taken September 25, 1951): penicillinase added, pour plate negative, culture negative. *September 23, 1951.* Blood cholesterol: 140 mg./100 ml.

The patient was seen in consultation on October 1, 1951. It was felt that his history left no reasonable doubt that pericardial effusion had been present for at least eight years. The consultant thought that the man's relatively good health, lack of febrile episodes, and absence of blood in the pericardial fluid made tuberculous pericarditis most improbable. Benign intrapericardial tumor was a possibility, but the probable diagnosis was chronic cholesterol pericarditis. He further thought that the man might be in a subacute phase of pericarditis preceding chronic constrictive pericarditis. In view of the reformation of fluid after several taps, and of the hazard of chronic constrictive pericarditis, pericardiectomy was considered. The consultant felt that the heart itself was probably normal.

On October 12, 1951, the patient was admitted to the Hospital of the Good Samaritan. An anterior pericardial tap was attempted on the day of admission; only 5 or 10 ml. of fluid were obtained. The next day a second pericardial tap was done laterally as well as posteriorly, and 1,350 ml. of fluid were obtained. Three hundred cubic centimenters of air were introduced. Subsequent x-ray films showed that all fluid had been removed. There was no evidence of pericardial tumor. Both of the physicians who performed the tap noticed resistance to the passage of the needle through the pericardium, and believed that considerable pericardial thickening was present, although x-ray evidence of this was slight. The hemogram was normal; the corrected sedimentation rate was 37 mm. in one hour. Examinations of the pericardial fluid (including gram stain, and cultures for fungi and *Mycobacterium tuberculosis*) yielded no additional information. In the fluid from these two taps no cholesterol crystals were observed. After the second tap the patient's temperature rose to 103° F., the leukocyte count rose to 19,200, and he complained of dyspnea. From physical examination, massive left pleural effusion was suspected, but x-ray revealed re-accumulation of pericardial fluid. A pericardial friction rub was noted throughout this hospital stay. At no time was there evidence of cardiac tamponade. Penicillin and streptomycin were administered. The patient was discharged on October 23.

The patient was re-admitted to the Hospital of the Good Samaritan on November 18, and on November 20 pericardiectomy was performed. The surgeon reported:

"The parietal pericardium was about one-eighth inch thick in its lower half, but on the upper half it was almost one-fourth inch thick. The pericardial scar stripped away from the epicardial scar with ease for the most part. The epicardial scar . . . was much thinner, and could be stripped away from the epicardial fat with ease. . . . When the epicardial scar was removed it was found to be very thin on the right side, but on the left side it was almost one-eighth inch thick and it became thicker as one progressed toward the pulmonary artery and the aorta. . . . The heart itself was definitely enlarged, its action quite regular throughout the operation in spite of manipulation. . . . All the fat surface of the epicardium appeared quite normal after decortication had been completed." The maximal postoperative temperature was 101° F. Fluid accumulated in the left pleural sac; the tap yielded 160 ml. of fluid. Subsequent films showed no re-accumulation of pleural fluid. On November 22 the patient became dyspneic, and the jugular veins were distended and pulsatile. The liver descended two finger breadths below the right costal margin and was tender. Purodigin, 1.2 mg., was administered on November 22, and 0.2 mg. on subsequent days. The response was prompt and favorable. The patient was discharged on November 30. An attending physician commented: "The reason for the cardiac enlargement is by no means clear to me. I have no better explanation to offer than that his pericarditis was associated with some degree of myocarditis."

The pathologist reported: "The sections of lymph node show hyperplasia. No tubercles seen. The many blocks of pericardium show inflammatory change with heavy fibrinous deposit at the surface. The inflammatory exudate consists of mononuclear cells, mostly lymphocytic. No tubercles or Aschoff bodies seen. A good deal of cholesterol deposition is present, often intermixed with fibrin and hematogenous pigment. In some areas there is inflammatory reaction about the cholesterin deposits with many macrophages and some giant cells present, often containing crystals. This component of the inflammatory or degenerative change is quite unusual. The origin of the cholesterin deposits is not clear unless it be the result of old repeated hemorrhages." (There was no evidence of old repeated hemorrhages.)

When seen in our office on December 6, 1951, the patient felt entirely well. His temperature was normal. The heart rhythm was regular at a rate of 86 per minute. The heart sounds were normal, and the blood pressure was 120/80 mm. of Hg. Fluoroscopically the left diaphragm was high and did not move. At the end of quiet inspiration the transverse diameter of the heart was 148 mm., the upper limit of normal being 140 mm. by the Kurtz application of the Hodges-Eyster formula. The electrocardiogram was strikingly different from that of June, 1951. There was marked right axis deviation. The T waves were inverted in Leads 1, 2, AVL and V_4 to V_6. Amplitude of the complexes was increased in all leads.

The patient was again examined on December 14, and the following notations made: "The electrocardiogram was repeated and was essentially the same as that made on December 6. . . . The right axis deviation and peculiar precordial leads are interpreted as being the result of extreme clockwise rotation of the heart despite its horizontal position."

On January 14, 1952, digitalis was discontinued. One month later the patient stated that he felt perfectly well and was working regularly. He was normotensive; there were no congestive phenomena. He was advised to follow a strict low-calorie diet.

On February 11, 1952, the blood cholesterol was 256 mg./100 ml. The patient was urged to avoid cholesterol-rich foods. On June 9 he weighed 174 pounds, a loss of 30 pounds since he was first seen a year before. His blood pressure was 130/80 mm. of Hg. The heart was somewhat smaller, its transverse diameter being 140 mm. by the Kurtz application of the Hodges-Eyster formula. Dexamyl tablets, one before meals, and a 1,000-calorie diet were prescribed. On October 20, 1952, the patient

weighed 166 pounds and seemed greatly improved. All medication was discontinued, and he was asked to report at yearly intervals.

On October 5, 1953, the heart was smaller, its transverse diameter being 135 mm. by the Kurtz application of the Hodges-Eyster formula. The blood pressure was 110/70 mm. of Hg.

There were no significant changes in 1954. On October 3, 1954, a chest x-ray was read as follows: "The heart is somewhat enlarged and appears to be pulled somewhat toward the left. The costophrenic angle is clear. . . . The apparent displacement of the heart may be the result of adhesions subsequent to the pericardiectomy in 1951. . . ."

The patient was admitted for study to the Glendale Sanitarium and Hospital on September 18, 1955. The blood cholesterol was 262 mg./100 ml. The protein-bound iodine was 4.4 μg./100 ml. An electrocardiogram was read as follows: "Right axis deviation, deep S waves in leads 1 and AVL, no S-T segment changes, inverted T waves in leads 1, AVL, V_1–V_6. Conclusion: Anterolateral myocardial ischemia or other disease; T wave inversions have appeared since 9-30-51, and the heart appears to be more vertically placed than formerly."

The patient was hospitalized again on September 28, 1956. The blood count and urinalysis were normal. The basal metabolic rate was minus 6%, and the protein-bound iodine was 4.3 μg./100 ml. The blood cholesterol was 204 mg./100 ml. A chest x-ray was interpreted as follows: "No change in the roentgenographic outline of the chest structures has developed since 9-12-55." An electrocardiogram was read as "posterior and lateral ischemia. . . ."

On December 12, 1957, a chest x-ray was read as follows: "The lung fields are clear. The heart shows left ventricular prominence. . . . The unusual appearance of the left border of the heart is, I believe, secondary to the pericardiectomy in 1951."

On April 20, 1959, the patient complained of a "cold" and right ear pain. The symptoms disappeared rapidly following oral antibiotic administration. A chest x-ray was interpreted as follows: "The heart shadow is smaller now. There still appears to be definite left ventricular prominence." An electrocardiogram on April 20, 1959, "shows a more normal pattern. There are no S-T segment changes. T waves are now normal in leads 2, AVF, V_1–V_3."

Since 1952 the patient has not lost a day's work because of illness. He avoids strenuous physical activity, but swims and plays golf.

Discussion

This is the fourteenth case of cholesterol pericarditis reported in the world literature, the sixth in American medical journals. Two of the cases (Daniel and Puder,[4] and Herzenberg and Fafius [5]) are probably not properly classified as idiopathic cholesterol pericarditis, since there was evidence of tuberculosis in one and of neoplasm in the other. The etiology in Creech's [2] patient may have been tuberculosis, since one of the pericardial fluid specimens showed *M. tuberculosis*.

Our patient is the first instance of successful treatment of cholesterol pericarditis by pericardiectomy. Whether, without surgery, he would have developed constrictive pericarditis (either concretio cordis, Pick's disease, or accretio cordis—mediastinopericarditis), we cannot know. Probably not, since at surgery there was no attachment of the pericardium to adjacent thoracic structures, and there was no fusing of the pericardium to the epicardium. In any case, pericardiectomy was indicated if only to free the heart from the mechan-

ical effects of massive pericardial effusion. (The fluid reformed after five pericardial taps.)

Why, after pericardial tap, does fluid reform in some cases of pericardial effusion and not in others? Do cholesterol crystals in themselves provoke reformation of fluid? Genecin's [3] cases (brothers) seem to support such a possibility. In the brother whose pericardial fluid contained cholesterol crystals, pericardiectomy was performed because fluid recurred after five pericardial taps. The other brother became asymptomatic after one pericardial tap yielding 200 ml. of fluid. He remained asymptomatic for three years. When he was last seen, the area of cardiac dullness was greatly increased to both the right and the left, but there was no change in the over-all cardiac size, and the electrocardiogram was normal.

The report of Ehrenhaft and Taber [6] provides experimental support for this concept. They injected crystalline suspensions of cholesterol into the pericardial sacs of two dogs. Both dogs later developed pericardial effusion, pericardial granulation tissue, and thickening of the pericardium and epicardium.

Many investigators have sought an explanation for the appearance of cholesterol crystals in serous fluids. The most likely hypothesis, summarized by Genecin,[3] is that deposition of cholesterol crystals may be the end result of disruption of soluble lipoprotein macromolecules over a long period of time. Since absorption from the pericardial surfaces is slow, ample time is usually provided. Like Genecin's first patient, ours showed cholesterol crystals only in the first three aspirates. This finding supports the concept that crystals appear only after slow degradation of lipoprotein complexes. If we concede this hypothesis, then why are cholesterol crystals not commonly found in other forms of chronic pericardial effusion?

The etiology and pathogenesis of cholesterol pericarditis remain obscure. In their review of the literature, Moe and Campos [1] conclude that while myxedema, pericardial effusion, and cholesterol pericarditis are often associated, the association is by no means automatic. There are instances (Feasby [7] and Gordon [8]) in which aspirated fluid from the pericardial sacs of patients with pericardial effusion accompanying myxedema revealed no cholesterol crystals. Moreover, administration of thyroid extract to persons with myxedema and pericardial effusion may bring about clinical recovery and disappearance of the effusion (Herrell and Johnson,[9] and Freeman [10]). Moe and Campos [1] believe their patient was euthyroid or hyperthyroid. Genecin's [3] first patient showed no clinical or laboratory evidence of thyroid dysfunction. Our patient exhibited no features of myxedema, although he may have been mildly hypothyroid.

There is no evidence for an infectious etiology. For the present we shall have to be content with the always unsatisfying adjective, "idiopathic."

Electrocardiograms sometimes show a pattern typical of pericarditis, but quite as often do not. Initial electrocardiograms in Moe's and Campos' [1] case, in Genecin's [3] first case, and in ours showed only low voltage. The explanation for postpericardiectomy changes may be that proposed by one of the consulting physicians (Dr. William Paul Thompson), *vide ante*. A more likely explanation is Genecin's: "These changes are thought to represent residual damage in the superficial layers of myocardium, possibly due to loss of pericardium or adhesions of the heart to the pleura."

Summary

A case is presented of idiopathic cholesterol pericarditis. The patient is the first successfully treated by pericardiectomy. Two others have been reported.[2, 3]

Since pericardiectomy in November, 1951, when he was 46 years of age, this man has enjoyed excellent health, and has continued his work (musician) without interruption.

The disease is rare but, with modern technics, highly curable. When in pericardial effusion the aspirated fluid shows a high content of cholesterol crystals, pericardiectomy will probably be the procedure of choice.

Summario in Interlingua

Solmente 12 casos de pericarditis a cholesterol se trova reportate in le litteratura medical del mundo. Quatro de istos es reportate in jornales american. Un del quatro esseva tractate a bon successo per pericardiectomia.

Le caso hic presentate es illo de un masculo qui habeva le prime symptomas de effusion pericardial probabilemente in 1943, al etate de 38 annos. Nos le videva primo in 1951.

Liquido se reformava post cinque paracenteses. Le prime tres aspiratos esseva cremose in apparentia e consistentia e habeva un alte contento de crystallos de cholesterol. Omne le aspiratos se provava culturalmente sterile. Inoculationes in porcos de India esseva negative pro bacillos acido-resistente.

Pericardiectomia esseva effectuate le 20 de novembre 1951, apparentemente le prime tractamento chirurgic pro pericarditis a cholesterol. (Duo alteres ha essite reportate depost ille tempore.) Le patiente se meliorava rapidemente e remarcabilemente. Le dimensiones del corde ha crescite, e le electrocardiogrammas nunc exhibi configurationes quasi normal. Depost 1952, le patiente non ha perdite un sol die de labor a causa de un maladia—ille es musico—e su conducta de vita es normal.

Pauco es cognoscite relative al etiologia o al pathogenese de iste condition. Varie hypotheses es revistate.

Pericarditis a cholesterol es rar sed apparentemente multo curabile. Pericardiectomia es probabilemente le methodo de election.

BIBLIOGRAPHY

1. Moe, A. S., Campos, F. J.: Cholesterol pericarditis. Ann. Intern. Med. **47**: 817–825, 1957.
2. Creech, O., Jr., Hicks, M., Jr., Snyder, H., Erickson, E. E.: Cholesterol pericarditis. Circulation **12**: 193, 1955.
3. Genecin, A.: Chronic pericardial effusion in brothers, with a note on "cholesterol pericarditis." Amer. J. Med. **26**: 496–502, 1959.
4. Daniel, G., Puder, S.: Perikarditis et pleuritis cholesterinae. Virchows Arch. f. path. Anat. **284**: 853, 1932.
5. Herzenberg, H., Fafius, G.: Ueber die xanthomatöse (cholesterin) perikarditis. Zentralbl. f. allg. Path. U. path. Anat. **46**: 97, 1929.
6. Ehrenhaft, J. G., Taber, R. E.: Hemopericardium and constrictive pericarditis. J. Thoracic Surg. **24**: 355, 1952.
7. Feasby, W. R.: Pericardial effusion in myxedema. Amer. Heart J. **19**: 749, 1940.
8. Gordon, A. H.: Some clinical aspects of hypothyroidism. Canad. Med. Ass. J. **20**: 7, 1929.
9. Herrell, G. T., Johnson, C.: Pericardial effusion in myxedema. Amer. Heart J. **25**: 505, 1943.
10. Freeman, E. B.: Chronic pericardial effusion in myxedema: report of case. Ann. Intern. Med. **7**: 1070, 1934.

SPONTANEOUS RUPTURE OF THE THORACIC AORTA THROUGH AN ATHEROMATOUS PLAQUE *

By Héctor F. Rodríguez, M.D., and Edwin Rivera, M.D., *Ponce, Puerto Rico*

Spontaneous rupture of the aorta is usually associated with aneurysm formation (luetic or arteriosclerotic in origin), or with dissection of the wall secondary to medial necrosis, with or without hypertension. It may also occur as a complication of congenital coarctation of the aorta.

The purpose of this report is to present a case of spontaneous rupture of the aorta in its thoracic portion through an atheromatous plaque. No evidence of aneurysm or dissection in the affected portion was found on post-mortem examination. As far as we could ascertain from the review of the literature and personal communications with recognized authorities on the subject, this is the first report of such a complication.

Case Report

A 58-year-old white woman was admitted to the Medical Service of the Ponce District Hospital, Ponce, Puerto Rico, on December 19, 1955, because of epigastric discomfort. She stated that for the last three to four months she had noticed vague epigastric discomfort which was not related to food intake, was more or less continuous, and was localized near the umbilicus, with radiation to the suprapubic region. In the previous two weeks she had noticed anorexia with occasional regurgitation of ingested food and, a few days prior to admission, vomiting. There was no history of food intolerance, melena or hematemesis, jaundice, diarrhea, or urinary symptoms. There had been no weight loss.

Previous history was essentially negative except for hypertension discovered several months before. On admission the temperature was 98.6° F.; pulse, 60; respiratory rate, 22; blood pressure, 160/130 mm. of Hg. The patient looked older than the stated age; she was in no acute distress, and was fairly well nourished. Head and neck examination was negative except for discrete cervical lymphadenopathy bilaterally, and mild engorgement of neck vessels. The chest was moderately emphysematous, but the examination of the lung fields was negative. The cardiac size was normal to percussion. On auscultation, a systolic murmur, grade 2, was heard at the apex. The aortic second sound was accentuated. Abdominal examination revealed a palpable pulsatile, and expansile mass about 5 cm. in diameter lying to the left of the umbilicus. The pulses were strong in both femoral arteries. Hardening and tortuosity of the peripheral vessels were noted. The neurologic examination was negative.

Laboratory studies revealed 2-plus albuminuria, with 40 to 50 red blood cells per high power field, 1 to 3 white blood cells, a few epithelial cells, and a specific gravity of 1.014. A repeat urinalysis showed 3-plus albuminuria on December 23, 1955, with 1 to 2 red blood cells per high power field. A complete blood count showed 3,900,000 red blood cells, with 88% hemoglobin, and a white blood cell count of 8,100, with 83% neutrophils, 14% lymphocytes, 2% basophils and 1% eosinophils. Stool examination was negative for occult blood and parasites. Blood serology was negative;

* Received for publication October 8, 1959.

From the Departments of Medicine and Pathology, Ponce District Hospital, Ponce, Puerto Rico.

Requests for reprints should be addressed to Héctor F. Rodríguez, M.D., 13 Mayor Street, Ponce, Puerto Rico.

a blood urea nitrogen was 12 mg.%. A chest plate (Figure 1) showed no significant abnormalities except for a healed Ghon complex in the left upper lobe and some elongation of the aorta. A flat plate of the abdomen revealed a small cluster of calcifications to the left of the third lumbar vertebra overlying the shadow of the left kidney. A barium enema was negative. An intravenous pyelogram (Figure 2) gave a better visualization of the previously described calcifications. They were seen not to be a cluster, as previously thought, but to form roughly an ellipse, with pointed ends. The contrast medium appeared bilaterally, outlining well the right kidney, where no abnormalities were observed. The left side was outlined only in very thin streaks, and visualization was not satisfactory in any of the films. The oval-shaped calcifications were interpreted as being a mass of vascular origin, located in part inferiorly and medially to the left kidney, and overlying it close to the area of the renal pelvis.

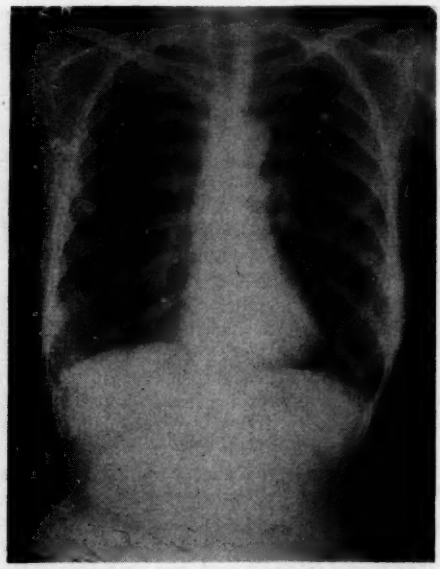


FIG. 1. Chest x-ray, showing a healed Ghon complex in the left upper lung and elongation of the aorta, with no other significant findings.

On January 13, 1956, while the patient was being studied for possible surgery of the suspected abdominal aortic aneurysm, she complained of severe left flank pain, and passed dark red urine. A urinalysis revealed hematuria. The next day the patient, who had been afebrile, developed spiking fever, which went up to 104° F. Penicillin, streptomycin and Gantrisin were given, and the fever subsided in 24 hours. The left flank pain slowly disappeared, and a repeat urinalysis on January 18 showed 1-plus albuminuria, a specific gravity of 1.016, 40 to 45 white blood cells per high power field, and 3 to 4 red blood cells.

On February 2, 1956, the patient had a sudden, massive hemoptysis (about 2,000 ml. of blood). She was found to be in shock, with an unobtainable blood pressure and a thready pulse. The cardiac auscultation was negative except for tachycardia. No other abnormalities were encountered. She was given blood and stimulants without avail, and died at 10:15 a.m. on February 2, 1956.

The clinical diagnosis was arteriosclerotic aneurysm of the abdominal aorta with dissection and rupture into the pleural cavity.

Post-mortem examination was performed two hours after death. In the thoracic cavity, the right pleural cavity contained no fluid and there were no adhesions. The left pleural cavity was partially obliterated in its lower half by loosely attached fibrinous deposits, and contained a large fresh blood clot between the diaphragmatic surface of the lung and the diaphragm. The left lower lobe was voluminous, firm, and dark red. In its posterior aspect it was firmly adherent to the thoracic aorta at a level of about 3 cm. above the diaphragm. When the lung was separated from the aorta, a tear was found in the latter at the site of the adhesions. The pericardium contained a small amount of clear fluid. The heart was contracted, and weighed 210 gm. The right atrium was neither dilated nor hypertrophied. The auricular

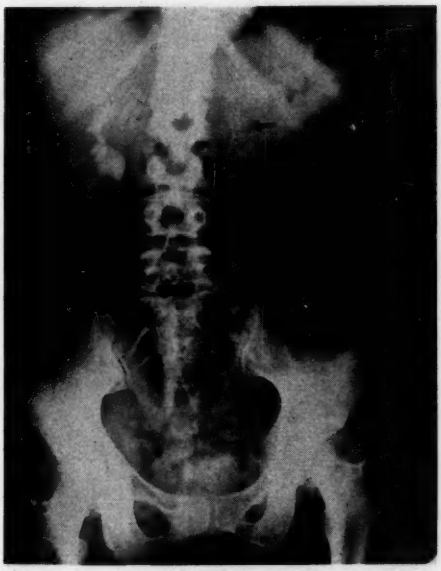


FIG. 2. Intravenous pyelogram, revealing normal visualization of right kidney. Arrows point to calcifications within a mass of vascular origin in the left side (abdominal aneurysm, arteriosclerotic).

appendage contained no thrombi. The tricuspid valve admitted three fingers and presented thin, transparent leaflets. The right ventricle and pulmonic valve were not remarkable. The pulmonary veins entered the left atrium in the usual way. The left atrium and auricular appendage were normal. The mitral orifice admitted two fingers. The valve leaflets showed scattered areas of thickening by yellowish tan, atherosclerotic plaques. The chordae tendineae showed the usual weblike insertions. The left ventricle showed moderately prominent papillary muscles and trabeculae. The endocardium was thin and transparent. The myocardium was reddish brown, firm and homogenous. Focal grayish white areas of fibrosis were noted in the tips of the papillary muscles. The aortic valve was not remarkable. The coronary ostia were patent. Scattered atheromatous plaques were seen in the coronary arteries.

The aorta presented numerous confluent, soft, atheromatous plaques which began

just above the aortic valve. At a level of 12 cm. distal to the left subclavian artery, an irregular defect, 1.5 cm. in diameter (Figures 3 and 4), was noted in the left side of the wall of the aorta. The defect was surrounded by soft, atheromatous plaques, and was located at the same level as the remaining aorta. No aneurysmal dilatation or dissection was noted at this site. There was thickening of the wall surrounding the defect, and it was found to be moderately adherent to the parietal and visceral pleura of the left lung. On section, the thickened tissue was grayish white. A large, partially organized clot was seen to protrude from the defect and to displace the pulmonary parenchyma, causing a hemispheric depression 7 cm. in diameter in the left lower lobe. Near the center of this depression there was a defect in the pulmonary parenchyma which measured 2 cm. in diameter. From this, a large fresh blood clot was found extending into the lower half of the left lower lobe. The

FIG. 3. The site of rupture of the thoracic aorta is marked with an arrow. Near the lower end of the picture the intact abdominal aortic aneurysm is also seen.

defect in the aorta was found at a level of about 2 cm. above the diaphragm. The remaining aorta showed moderately severe atherosclerosis. In the abdominal aorta, about 3 cm. proximal to the bifurcation, there was an aneurysmal dilatation in the right anterolateral aspect (Figure 3). The dilatation measured 5 by 4 cm. in its greatest dimensions. The left subclavian artery was occluded by a soft, adherent, reddish gray mass. The remaining vessels arising from the aorta were patent and showed moderate atherosclerosis.

The lungs weighed 1,000 gm. together. The right lung and the upper lobe of the left lung were hypercrepitant and collapsible. Scattered subpleural emphysematous blebs were noted. The left upper lobe was firm, dark red and voluminous. Fibrinous deposits were found on the pleura. In its lower half, in the mediastinal surface, it presented a depression (see aorta), which was covered by a thickened, opaque pleura. Large blood clots within the left lower lobe had partially dissected the pulmonary

parenchyma. Small bronchial branches and vessels had been torn. The remaining parenchyma revealed severe congestion. The bronchi of both lungs contained blood clots and blood-stained mucus. The trachea was patent, and the larynx was not remarkable. The pulmonary arteries and veins were normal.

The liver weighed 1,000 gm. and was moderately firm, and the capsule showed scattered areas of thickening in the anterior surface. The parenchyma and lobular pattern were normal. The gall-bladder was distended, and a few soft calculi were found within the lumen and neck. The cystic duct was patent, and no calculi were seen in the hepatic or common ducts.

The spleen weighed 40 gm. and was normal in appearance. A small accessory spleen was found attached to the pericolonic tissue at the splenic flexure. The pancreas, adrenals, and gastrointestinal system were not remarkable.

FIG. 4. A closer view of the area of rupture. The atheromatous plaques within the aortic wall are clearly seen.

The right kidney weighed 100 gm., and the left, 110 gm. The capsules were slightly adherent, and the surfaces were granular and red. The corticomedullary junction was well demarcated. The cortices were slightly narrower than usual, and showed a fine granularity. The medullae were dark red. The pelves and calyces were not remarkable, except for focal hemorrhages in the mucosa. The ureters followed their usual course without obstruction or dilatation. The urinary bladder showed a smooth mucosa. The uterus was small and the ovaries were atrophic. The tubes were not remarkable.

Microscopic Examination: Significant pulmonary findings were limited to extensive intra-alveolar hemorrhage. Sections of the aorta through the site of rupture and elsewhere failed to reveal medial necrosis or any other underlying basic pathologic process to explain the rupture. The kidneys showed arteriosclerosis, with focal cortical scars and hydropic degeneration.

Discussion

The aorta, in its role as the largest conducting vessel of the arterial system, is subject to great changes in pressure as the heart contracts and relaxes. To withstand this stress, its media possesses a large amount of elastic tissue. Attempts to rupture healthy aortas of rabbits or humans experimentally have been unsuccessful, even when great pressures were exerted.[1] Thus, rupture of the aorta not associated with trauma normally occurs only after prolonged weakening of its wall, as in aneurysm formation, or when cystic medial necrosis produces a dissecting aneurysm.

Aortic aneurysms of arteriosclerotic origin are believed to occur by the dislodgment of an atheromatous plaque with ulcer formation, or when extravasation of blood beneath a plaque causes a tear in the intima. The intravascular pressure exerted on the media gradually leads to weakening of its wall, producing a bulge and, thereafter, an aneurysm. The patient presented had such a complication in the abdominal aorta, its presence being the reason for her admission. However, on post-mortem examination the aneurysm was found to be intact, no rupture or dissection having occurred. Higher up, in the thoracic aorta, in an area where the only pathologic finding was atherosclerosis, a spontaneous rupture of the entire wall through an atheromatous plaque had occurred, resulting in massive hemorrhage and death. When the site of rupture was found, careful evaluation of the area of the defect was carried out. We have failed to demonstrate any developmental anomaly in the affected area, and no evidence of gradual extravasation through the coats of its wall. Apparently, there had been a simultaneous and complete rupture of the entire wall at the site of an atheromatous plaque.

Summary

1. A case has been presented of spontaneous rupture of the thoracic aorta through an atheromatous plaque, without aneurysm or dissection at the site of rupture. The patient died from severe hemoptysis when the aorta ruptured into the pleural cavity, the blood penetrating the left lower lung, with destruction of the pulmonary parenchyma. An abdominal aneurysm of arteriosclerotic origin was also found, but it was intact.

2. As far as we could ascertain, this is the first reported case of such a complication. No explanation for the spontaneous tear of the entire aortic wall could be found at post-mortem examination.

Summario in Interlingua

Rupturas spontanee del aorta es usualmente associate con formationes aneurysmic —de origine luetic o arteriosclerotic—o con dissectiones parietal secundari a necrosis medial. Illos etiam occurre como complication de coarctation del aorta.

Es reportate un caso de ruptura spontanee del aorta thoracic via un placa atheromatose, sin aneurysmo e sin dissection. Le patiente, hospitalisate a causa de un aneurysmo arteriosclerotic abdominal, moriva subitemente post hemoptysis massive.

Le necropsia revelava que un ruptura del aorta thoracic habeva occurrite 2 cm supra le diaphragma, con le resultato de un massive hemorrhagia. Le sanguine penetrava in le pulmon sinistro-inferior, resultante in le destruction del parenchyma pulmonar. Sectiones del aorta a transverso le sito del ruptura e alterubi non revelava

signos de necrosis medial o ulle altere processo pathologic capace a explicar le occurrentia del ruptura. Un aneurysmo abdominal de origine arteriosclerotic esseva trovate, sed illo esseva intacte.

In tanto que il esseva possibile determinar per un scrutinio del litteratura e per le consultation personal de autoritates in iste campo, le presente caso es le prime unquam reportate de un tal complication. Nulle explication del fissura spontanee del integre pariete aortic esseva trovabile in le examine necroptic.

BIBLIOGRAPHY

1. Klotz, O., Simpson, W.: Spontaneous rupture of the aorta. Amer. J. Med. Sci. **184**: 455, 1932.

PARALYTIC ILEUS SIMULATING ACUTE INTESTINAL OBSTRUCTION DUE TO PENTOLINIUM TARTRATE (ANSOLYSEN) *

By Kenneth L. Becker, Captain (MC), and
Alton I. Sutnick, Captain (MC) †

In recent years pentolinium tártrate has become one of the most widely used drugs in the treatment of severe hypertension. The case described below illustrates dramatically a side effect of this drug, ileus mimicking acute intestinal obstruction, a result of pentolinium-induced parasympatholysis.

Case Report

The patient was a 58-year-old white retired Army officer with known hypertension of eight years' duration. Two years prior to admission he had noticed the onset of intermittent claudication, occasional nosebleeds, dyspnea on effort, orthopnea, and occasional angina. At one time he experienced a sudden coldness of his left leg lasting several hours. He had nocturia twice nightly. Intravenous pyelography at this time showed very poor concentration of dye, and his blood urea nitrogen varied between 27 and 45 mg.%. His hypertension was being treated with reserpine and hydralazine, and his average blood pressure was 240/140 mm. of Hg. Failure of these drugs to control his blood pressure was considered to be evidence of early malignant hypertension, and hydralazine was replaced by pentolinium, 80 mg. three times a day.

Ten days later the patient was admitted to the hospital with complaints of dizziness, constipation, and vomiting. His abdomen was found to be distended and tympanitic, but bowel sounds were normal. His blood pressure was 140/80 mm. of Hg. Abdominal radiography revealed moderate gastric dilatation. Medication was stopped, and the patient's symptoms were relieved by the next day with a regimen of bed-rest, a soft diet, and mineral oil. His blood pressure rose to 190/110 mm. of Hg. Several weeks following his discharge, pentolinium therapy was reinstituted. Constipation was avoided with various laxatives and, if it returned, pentolinium

* Received for publication September 17, 1959.
† From 196th Station Hospital, Neuilly-sur-Seine, Paris, France.
Requests for reprints should be addressed to Kenneth L. Becker, M.D., 427 Seventh Avenue, Southwest, Rochester, Minnesota.

dosage was lowered accordingly. For the next 20 months the patient received pentolinium in doses varying between 40 and 70 mg. three times daily, a low-fat, salt-poor diet, Priscoline, 50 mg. three times a day, and reserpine, 0.25 mg. four times a day. He did quite well clinically, showing no significant progression in his hypertensive process, and his blood pressure now averaged 160/100 mm. of Hg.

Two days prior to his final admission the patient noted the onset of constipation. The following day he had several small, watery stools, and became increasingly anorexic towards evening. On the morning of the day of admission the diarrhea was persistent; the patient vomited several times, felt very weak, and noted progressive abdominal swelling associated with a continuous right upper quadrant abdominal pain. There was no history of hematemesis or grossly bloody stools.

Physical examination revealed an obese man of elderly appearance, constantly complaining of abdominal pain. His temperature orally was 99.5° F.; pulse, 60; blood pressure, 90/60 mm. of Hg. A prosthesis replaced the right eye, which had been lost because of a war injury. The fundus of the left eye was obscured by a fixed, constricted, scarred pupil. His heart was slightly enlarged to the left by percussion. No cardiac murmurs were heard, and his lungs were clear to percussion and auscultation. His abdomen was extremely distended and tympanitic, and was generally tender on deep palpation, but there was no muscle guarding. No masses were palpated. Bowel sounds were hyperactive. Examination of the lower extremities revealed varicose veins and weak femoral arterial pulsations; no pulse was obtainable below the femorals. Rectal digital examination was normal. A complete blood count and urinalysis were within normal limits, as were the serum electrolytes. Blood urea nitrogen was 42 mg.%. Chest x-ray revealed slight widening of the transverse diameter of the heart and a somewhat dilated aorta. An abdominal flat plate showed a greatly dilated stomach and gaseous distention of the intestines, primarily the small bowel. An electrocardiogram showed left axis deviation, left ventricular hypertrophy, and signs of an old posterior myocardial infarction.

The abdominal pain was relieved quickly by means of Demerol administration and gastric intubation. The major diagnostic possibilities at that time were pentolinium intoxication and mesenteric artery occlusion. Continuous norepinephrine infusion at first maintained his blood pressure, but soon it was observed that larger and larger dosages were required. Inasmuch as the patient was proceeding on a downhill course despite treatment with gastric suction, electrolyte replacement, blood transfusion, and norepinephrine, surgical exploration was considered. A change in the character of peristalsis, suggesting obstructive rushes, strengthened this opinion, and exploratory laparotomy was performed.

At operation, the stomach and small bowel down to the cecum were uniformly distended, and filled with gas and fluid. No distention of the large bowel was noted. The intestinal tract was systematically inspected, and no evidence of mechanical obstruction was found. There were no signs of mesenteric vascular occlusion, intestinal tumors, aortic aneurysm, or pancreatic pathology. Postoperatively the course was characterized by a continuous struggle to maintain the patient's blood pressure with norepinephrine and to relieve his ileus. Oxygen was administered and gastric suction continued. After laxatives, enemas, and large quantities of parasympathomimetic drugs the patient finally passed some flatus, and by 15 hours after surgery his abdomen was slightly less distended. However, despite adequate fluid replacement, the urine output was only 25 ml. during this period. Fluid intake was then curtailed, but the blood pressure fell even as the norepinephrine concentration was rapidly increased and hydrocortisone added to the infusion. The patient finally succumbed to the development of rapidly progressive pulmonary edema.

Post-mortem examination was limited to the thorax and abdomen. Gross findings included pulmonary edema, marked coronary sclerosis, evidence of old posterior

myocardial infarction, slight hypertrophy and dilatation of the left ventricle, a distended small intestine, and a congested gastric mucosa. The abdominal aorta was atherosclerotic, but there were no signs of occlusion of the mesenteric vessels. A small accessory spleen was found. Microscopic results included intense congestion of the stomach and ileum, with no evidence of bowel ulceration or inflammatory change, and signs of an old chronic pyelonephritis. There was no pathologic alteration of the lumbar sympathetic ganglia, and no degenerative changes were found in the neural tissue of the intestines.

Discussion

Pentolinium is a member of the ever-growing family of quaternary ammonium compounds which block nerve transmission across autonomic ganglia. Essentially, the members of this group differ from one another only in their duration of action, percentage and speed of absorption, and possibly in their effectiveness at different ganglia.[1, 2] As Schroeder [2] states, when we give these drugs to a patient we cause sympatholysis at the price of parasympatholysis. Pentolinium produces, in effect, a medical sympathectomy and partial parasympathectomy.[3] Constipation often occurs as a result of this partial parasympathetic blockade. In an early clinical appraisal of pentolinium, Freis found an incidence of constipation of 40% among his patients.[1] The great danger of this complication is that the drug stays longer in the intestinal tract, exposed to prolonged absorption; pharmacologic action is thereby augmented and prolonged.[3] Consequently, constipation is to be carefully avoided by judicious use of laxatives and parasympathomimetic drugs.[4, 5]

To the authors' knowledge, this is the third reported case of paralytic ileus due to pentolinium tartrate, and the second case simulating acute intestinal obstruction. In a study of pentolinium by Freis,[1] one of his patients, who had had severe bouts of gastric dilatation when taking hexamethonium, suffered a similar attack when taking pentolinium. Gifford et al.[6] noted paralytic ileus in a man 61 years old who had taken pentolinium, 240 mg. three times daily, for one week. The ileus subsided with conservative management, and pentolinium therapy was reinstituted. He never subsequently needed a laxative, in spite of the fact that he was later taking 300 mg. four times daily. Gibson [7] reported the case of a 58-year-old man who was taking 40 mg. of pentolinium three times daily and who was hospitalized with an ileus simulating acute intestinal obstruction. This patient presented with abdominal pain, distention, vomiting, and a blood pressure of 90/70 mm. of Hg. No constipation was noted until the onset of the acute abdominal pain. Abdominal x-ray film revealed distended loops of small bowel with some fluid levels. The patient was treated conservatively with intravenous fluids and stomach aspiration, and recovered.

In contradistinction to the "classic" description of paralytic ileus, the ileus caused by ganglionic blockade often causes abdominal pain. The severe pain in our patient was continuous and right upper quadrant in location. Gibson's [7] case had severe colicky lower abdominal pain. Ettman et al.[8] reported on a patient with hexamethonium intestinal ileus causing cramping upper abdominal pain. Goldstone [9] reported a patient with pentamethonium bromide ileus, with the clinical and radiologic picture of obstruction and with hypogastric pain. It is of interest that, in Goldstone's patient, the diagnosis of mesenteric thrombosis also was entertained. The hexamethonium ileus case of Thomas

and Williams [10] had colicky central abdominal pain. Bourne and Hosford [11] described a patient who underwent exploratory laparotomy for hexamethonium ileus, and mentioned that abdominal pain was present. Goldsmith [12] noted the presence of colicky abdominal pain in his case of hexamethonium ileus, and Lyons and Lord [13] reported colicky epigastric pain in their patient. Grant and Boyd [14] described two cases of mecamylamine-induced ileus masking as a surgical emergency, and presenting abdominal pain as a prominent feature of the clinical picture. McCalla et al.[15] reported on two patients with hexamethonium ileus, one with severe colicky abdominal pain, the other with generalized abdominal tenderness. The latter patient developed localization of the pain to the right midabdomen, and right lower quadrant muscle spasm led to operative intervention, with the tentative diagnosis of acute appendicits. Abdominal pain was also encountered in two of the mecamylamine ileus cases described by Furste et al.[16] and the two of Waldron.[17]

As seen in our patient, paralytic ileus may be heralded initially by diarrhea.[18] This was also a feature of both hexamethonium ileus patients of Lyons and Lord,[13] and the one of Mackey and Shaw.[19] Freis and Wilson,[20] in evaluating mecamylamine, discontinued treatment in four patients because of abdominal distention either with obstipation or with small, frequent liquid stools. Waldron [17] described a similar clinical picture, due to mecamylamine, in which the patient had been having two or three watery stools each morning.

One of the important considerations in operating on our patient was the continuous presence of peristaltic sounds. In the case of pentolinium ileus described by Gibson,[7] borborygmi were also heard. It is of interest that one of the first reported cases of ileus due to hexamethonium persisted to a greater or lesser extent for more than three weeks, and bowel sounds were present at all times.[10] The hexamethonium ileus case of Mackey and Shaw [19] exhibited occasional faint bowel sounds, and a patient of McCalla et al.[15] had hyperactive peristalsis with high-pitched bowel sounds. Both of the patients of Grant and Boyd [14] with mecamylamine ileus presenting as a surgical emergency had bowel sounds. Furste et al.[16] describe a patient with mecamylamine ileus who had hyperactive intestinal sounds. Both of the mecamylamine ileus emergencies described by Waldron [17] had hypoactive bowel sounds, but one had occasional high-pitched rushes.

In our patient and in most of the previously reported cases of an intestinal obstruction-like syndrome due to ganglionic blockade, the gaseous distention predominantly involved the proximal bowel, and radiography or laparotomy revealed the large intestine to be spared or minimally involved.[7-9, 11, 12, 14, 16, 17, 19, 21]

Restoration of bowel activity, once it has been paralyzed by parasympatholysis is, as Estes [18] states, somewhat like whipping a tired horse, for one is trying to stimulate ganglia which have been depressed by the ganglionic blocking drug. As illustrated in our case, this refractoriness of the bowel to stimulation may be of grave consequence. The danger of the appearance of ileus during pentolinium or other ganglion blocking therapy should be greatly diminished in the future, since Freis et al.,[22] as well as many others, have demonstrated that administration of chlorothiazide to hypertensive patients potentiates these drugs, and leads to reductions in their dosages averaging 40%, thus resulting in a concomitant reduction in side effects.

It can be seen, therefore, that paralytic ileus due to pentolinium or other ganglionic blocking drugs can easily masquerade as a surgical emergency because of its atypical features. Since patients taking these medications often represent the less desirable surgical risks, the importance of considering this syndrome in hypertensives with an "acute abdomen" is obvious.

Summary

A case is presented of pentolinium tartrate-induced ileus clinically manifesting itself as an acute surgical intestinal obstruction. It is emphasized that this patient developed the ileus suddenly, with only one day of immediately preceding constipation, followed by diarrhea. It is of diagnostic importance that abdominal pain is often a prominent feature of the symptomatology of ileus caused by ganglion blocking agents, and that the gaseous distention quite often will not extend to any considerable degree beyond the small intestine. In addition, it is emphasized that the presence of audible peristalsis is not at all unusual and should not rule out the diagnosis.

Summario in Interlingua

Es presentate un caso de intoxication per tartrato de pentolinium, resultante in ileus con symptomas simulante acute obstruction intestinal. Le patiente esseva un masculo de racia blanc de 58 annos de etate con le anamnese de octo annos de hypertension. Duo annos ante le hospitalisation, le symptomas del hypertension habeva devenite marcatemente plus grave, con le tension de sanguine medie attingente un nivello de 240/140 mm de Hg. A ille periodo, pentolinium esseva addite al programma therapeutic. Intra dece dies le patiente disveloppava vertigine, constipation, e vomito. Istos esseva alleviate per discontinuar le curso de pentolinium e per initiar appropriate mesuras contra le constipation. Le uso de pentolinium redeveniva necessari pro combatter le continuemente montante tension de sanguine. A generalmente parlar, le procedura esseva successose. Duo dies ante le hospitalisation, un episodio de constipation esseva sequite de diarrhea. Anorexia, nausea, e vomito superveniva; le abdomine se inflava progressivemente; e le patiente disveloppava dolores in le quadrante dextero-superior.

Le examine physic al tempore del admission al hospital demonstrava un frequentia del pulso de 60 e un tension de sanguine de 90/60 mm de Hg. Le abdomine del patiente esseva distendite e hyperesthetic. Le activitate peristaltic esseva plus que normal. Le studios laboratorial revelava le valor anormal de 42 mg% pro nitrogeno del urea del sanguine. Le electrocardiogramma produceva evidentia de un ancian infarcimento postero-myocardial. In le radiogramma del abdomine, le stomacho e le intestino tenue esseva dilatate.

Le tension de sanguine continuava su descendita, e le sonos intestinal disveloppava un character tintinante que suggereva le presentia de un obstruction organic. Le administration de norepinephrina e de liquidos intravenose, le effectuation de suction gastric, e transfusiones de sanguine non succedeva a arrestar le continue descendita del tension de sanguine. Esseva effectuate un laparotomia exploratori, sed nulle indicio de un obstruction esseva trovate. Post le operation, le tractamento consisteva de vasopressores, parasympathomimeticos, hydrocortisona, e le meticulose regulation del economia electrolytic, sed le persistentia de ileus e hypotension e le supervenientia final de oliguria resultava in le morte del patiente. Le autopsia revelava dilatation del stomacho e del intestino tenue. Le altere constatationes

esseva illos de un sever morbo cardiovasculo-renal de origine hypertensive arteriosclerotic.

Isto es le secunde reportate caso de ileus per pentolinium simulante acute obstruction intestinal. Le droga frequentemente produce constipation in consequentia de su effecto parasympatholytic. Como in le caso del presente patiente, ileus ab blocage ganglionic es frequentemente le causa de dolores abdominal, per contrasto con le caso usual de ileus paralytic. Persistentia de sonos peristaltic es etiam un aspecto atypic, e in le majoritate del reportate casos le distension gasose concerne predominantemente le intestino tenue. Es etiam a notar que diarrhea pote esser presente a un periodo precoce in le curso de ileus paralytic. A causa de iste characteristicas, le importantia es sublineate de prender in consideration le possibilitate de intoxication per drogas ganglio-blocante in casos de hypertension con "abdomine acute."

BIBLIOGRAPHY

1. Freis, E. D., Partenope, E. A., Lilienfield, L. S., Rose, J. C.: A clinical appraisal of pentapyrrolidinium (M&B 2050) in hypertensive patients. Circulation **9**: 540, (Apr.) 1954.
2. Schroeder, H. A.: Hypertensive vascular disease: therapy with modern drugs and its limits. J. Chron. Dis. **1**: 497 (May) 1955.
3. Sheldon, M. B.: The status of present-day drug therapy of hypertension. Amer. Practit. **7**: 33 (Jan.) 1956.
4. Gunn, J. A., Cooke, A. M.: Pilocarpine as an antagonist to the undesired effects of ganglion-blocking agents in the treatment of hypertension. Brit. Med. J. **1**: 1473 (June 26) 1954.
5. Waldman, S., Pelner, L.: Treatment of the ambulatory hypertensive patient with pentolinium tartrate. Amer. J. Med. Sci. **231**: 140 (Feb.) 1956.
6. Gifford, R. W., Allen, E. V., Birkhead, N. C.: Pentapyrrolidinium observations. Proc. Mayo Clin. **29**: 496 (Sept. 1) 1954.
7. Gibson, D. S.: A case of intestinal obstruction following the administration of pentapyrrolidinium bitartrate ("Ansolysen"), Med. J. Aust. **2**: 860, 1957.
8. Ettman, I. K., Bouchillon, C. D., Halford, H. H.: Gastrointestinal roentgen findings due to untoward effects of hexamethonium. Radiology **68**: 673 (May) 1957.
9. Goldstone, B.: Death associated with methonium treatment. S. Afr. Med. J. **26**: 552 (July) 1952.
10. Thomas, O. M., Williams, R. G.: Paralytic ileus after hexamethonium. Brit. Med. J. **1**: 1331 (June 9) 1951.
11. Bourne, G., Hosford, J.: Methonium compounds in hypertension; letter to the editor. Lancet **1**: 527 (Mar. 3) 1951.
12. Goldsmith, H. J.: Death from hexamethonium ileus. Brit. Med. J. **1**: 522 (Feb. 26) 1955.
13. Lyons, W. G., Lord, P. J.: Paralytic ileus after hexamethonium. Brit. Med. J. **2**: 176 (July 21) 1951.
14. Grant, A. P., Boyd, J. S.: Mecamylamine ileus as a surgical emergency. Lancet **1**: 713 (Apr. 6) 1957.
15. McCalla, L. H., Creech, O., Jr., Ford, R. V.: Hexamethonium ileus. Amer. Surg. **19**: 115 (Feb.) 1953.
16. Furste, W., Phelps, D., Taylor, P.: Antihypertensive drugs as a cause of the acute abdomen. J. A. M. A. **166**: 2111 (Apr. 26) 1958.
17. Waldron, J. F.: Ileus due to mecamylamine hydrochloride simulating an acute surgical condition of the abdomen. Minnesota Med. **41**: 499 (July) 1958.
18. Estes, J. E.: Hypertension in 1958: a tale of pills, philosophy, and perplexity. Med. Clin. N. Amer. **42**: 899–915, 1958.

19. Mackey, W. A., Shaw, G. B.: Paralytic ileus after hexamethonium. Brit. Med. J. 1: 1205 (May 26) 1951.
20. Freis, E. D., Wilson, I. M.: Mecamylamine, a new, orally effective, hypotensive agent. Arch. Intern. Med. 97: 551 (May) 1956.
21. Freis, E. D., Finnerty, R. A., Schnaper, H. W., Johnson, R. L.: The treatment of hypertension with hexamethonium. Circulation 5: 20 (Jan.) 1952.
22. Freis, E. D., Wilson, I. M., Parrish, A. E.: Enhancement of antihypertensive activity with chlorothiazide. Circulation 16: 882 (Nov.) 1957.

HEMOBILIA: REPORT OF A CASE OF MASSIVE GASTROINTESTINAL BLEEDING ORIGINATING FROM A HEPATIC ABSCESS *

By John H. Karam, M.D.,† and Theodore Jacobs, M.D.,‡
San Francisco, California

Bleeding into the biliary duct system has been classified into two general types, extrahepatic and intrahepatic, according to the site of hemorrhage.[1-3] The intrahepatic type, although rare, has been reported from traumatic rupture of the liver;[4-12] vascular lesions of the hepatic artery, including vasculitis,[13] hemangiomata,[1] and aneurysm;[14] neoplasms;[15,16] and yellow atrophy of the liver, both acute[17] and subacute.[1]

In 1948 Sandblom,[4] in an excellent clinical review, introduced the term "hemobilia" to describe bleeding into the biliary tract. He noted that hemobilia, regardless of cause, is usually manifested by severe pain in the upper right quadrant of the abdomen, suggesting biliary colic, distention of the gall-bladder, hematemesis, and melena. Although not common, hemobilia should be suspected in any case of unusual gastrointestinal bleeding accompanied by severe "colicky" abdominal pain.

The case described in this paper is believed to be the first reported instance of fatal hemobilia due to a hepatic abscess.

Case Report

The patient, a 92-year-old male Chinese, was admitted for the second time to H. C. Moffitt Hospital in a state of cardiovascular shock on October 22, 1958. According to his account, he had suffered during the last four years from recurrent postprandial abdominal pain which was aggravated by fatty foods. An oral cholecystogram taken elsewhere in March, 1955, had reportedly shown "poor filling," but no evidence of cholelithiasis. No abnormalities had been found by x-ray examination of the upper gastrointestinal tract, and no history of jaundice could be elicited. The

* Received for publication October 5, 1959.
From the Department of Medicine, University of California School of Medicine, San Francisco, California.
† Present address: Postgraduate Medical School, London, England.
‡ Present address: Captain Theodore Jacobs (MC), 29457H, 3970th USAF Hospital (Box 4326), APO 283, New York, N. Y.
Requests for reprints should be addressed to the Editorial Office, Department of Medicine, University of California Medical Center, San Francisco 22, California.

pain was fairly well controlled by administration of antispasmodics and a low fat diet until March, 1958, when epigastric discomfort became increasingly severe, and melena and massive hematemesis occurred. The patient was admitted to another hospital in a state of shock; the hemoglobin concentration was 4.3 gm. per 100 ml. X-ray barium studies showed a large, presumably active ulcer crater in the first part of the duodenum. The patient was given numerous transfusions of whole blood. On the third day of hospitalization he suffered a myocardial infarction, complicated by acute left ventricular failure, necessitating digitalization. He was transferred to the H. C. Moffitt Hospital on March 25, where he convalesced uneventfully until his discharge 24 days later. At that time his hematocrit had risen to 43%.

The patient remained essentially asymptomatic during the next six months. He again developed colicky pain in the right hypochondrium which became progressively more severe, necessitating his re-admission to the hospital on October 22. No nausea, vomiting, diarrhea, gastrointestinal bleeding, chills or fever, jaundice, chest pain, trauma, or exposure to any noxious agent or drugs had preceded the attack.

On physical examination the patient appeared to be critically ill and in shock. His blood pressure was 60/40 mm. Hg; pulse, 120 beats per minute and weak; temperature, 39° C. orally. Scleral icterus was observed. His abdomen was moderately distended and markedly tender; voluntary muscular guarding was noted over the right upper quadrant. The liver and spleen were not palpable, and no abnormal masses were felt, but bowel sounds were diminished. Otherwise, no physical abnormalities were found.

Results of laboratory studies were as follows: hematocrit, 45%; white blood count, 22,500 cells per cubic millimeter, with 86% neutrophils and a decided shift to the left. Urinalysis yielded positive reaction for bile but was otherwise negative; stools were guaiac-negative. Serum bilirubin totaled 6.4 mg. per 100 ml.; serum amylase was within normal limits. An x-ray film of the abdomen showed generalized ileus, but no free air. Nonspecific ST and T wave abnormalities were shown in the electrocardiogram, but except for evidence of sinus tachycardia, the tracing was not significantly different from one taken in April. Material obtained by gastric aspiration was slightly guaiac-positive.

Although the packed cell volume was normal, the patient's previous history of duodenal ulcer and his current state of peripheral vascular collapse suggested the possibility of acute gastrointestinal hemorrhage. He was given a transfusion of 2 units of whole blood which, although producing no clinical evidence of improvement, resulted in a rise in the hematocrit to 52%.

The lack of response to transfusion and the absence of signs of bleeding during the next 24 hours favored a diagnosis of cholecystitis or cholangitis, and possibly an associated bacteremia. Accordingly, penicillin, 2,400,000 units, and streptomycin, 1 gm., were administered daily. Because of his critical condition, hydrocortisone, 80 to 100 mg. daily, was injected parenterally during the first week. Large daily doses of metaraminol and phenylephrine failed to raise the patient's systolic pressure satisfactorily. To keep the patient's blood pressure above 100 mm. Hg systolic, and to maintain a normal output of urine, it was necessary to administer levarterenol, 20 μg. per minute, via the femoral vein. Additional therapeutic measures consisted of administration of oxygen, use of gastric aspiration, and attention to fluid and electrolyte balance.

During the next three days the patient continued to have fever, persistent pain in the right upper quadrant of the abdomen, and increasing icterus. On the second day a generalized purpuric rash appeared abruptly on the skin and mucous membranes; it was associated with a blood platelet count of 27,000 per cubic millimeter and a prothrombin time of 16.5 seconds (33%). Ivy bleeding time and Lee-White clotting time were within the limits of normal, however, and there was no clinical

evidence of blood loss. By the third hospital day the serum bilirubin had risen to 10.8 mg. per 100 ml. (direct bilirubin, 5.4 mg. per 100 ml.), and urinary urobilinogen was present in a titer of 1:80. Alkaline phosphatase was 11 units (Shinowara-Jones-Reinhart method; normal, 2 to 6 units), and cephalin-cholesterol flocculation was 3-plus. Serum proteins were normal.

The patient began to show clinical improvement on the fourth hospital day. By the sixth day he was afebrile, the rash had cleared, icterus had diminished, and platelet count and prothrombin time had returned to normal. An electrocardiogram showed no further changes. Urinary output continued to be adequate. On the eighth hospital day levarterenol was withdrawn without decrease in the blood pressure. Hydrocortisone was reduced in dosage the same day, and was discontinued entirely on the following day. Abdominal pain and tenderness had decreased con-

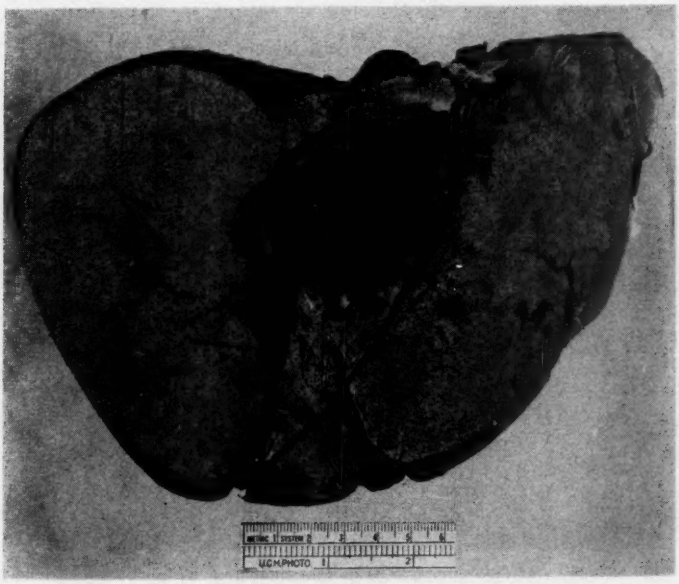


FIG. 1. Cut section of liver. The well circumscribed hematoma-abscess cavity is shown flanked by intact branches of the hepatic vein.

siderably. In the interim, serum bilirubin had dropped to 4.6 mg. per 100 ml. and alkaline phosphatase to 4 units. Although cultures of blood drawn on the day of admission had been reported as negative, antibiotic therapy was continued. The patient continued to improve slowly until the afternoon of the tenth hospital day, when he suddenly developed intense, colicky abdominal pain. Approximately one hour later he had a massive gastrointestinal hemorrhage, accompanied by both melena and hematemesis, which resulted in hypovolemic shock and a drop in the hematocrit to 34%. Rectal temperature rose to 38.6° C. The patient's abdomen became rigid, but was only slightly tender to palpation. No increase in jaundice was evident. Over the next 36 hours the patient passed numerous liquid tarry stools, and bright red blood appeared in the gastric aspirate. Despite repeated transfusions of whole blood the patient's condition rapidly worsened, and death occurred on the twelfth hospital day.

Post-mortem Findings: The pertinent findings were limited to the abdomen and the hepatobiliary system. The peritoneal cavity contained approximately 1,000 ml. of freshly clotted blood, located mainly in the superior portion but found also in the lesser and greater peritoneal sacs. The peritoneum showed no inflammatory changes or adhesions. The stomach and the small and large intestines were distended with fresh blood. The mucosal surface of the entire intestinal tract was examined and found to be intact; no petechiae, ulcerations, varices, perforations, or evidence of generalized capillary bleeding could be detected. A fibrosed scar of a completely healed ulcer was seen in the duodenum, but no active ulcers were present.

The liver, weighing 1,450 gm., was pallid but otherwise appeared to be normal. On section, however, a fairly well circumscribed cavity, measuring 5 by 4 by 4 cm. and containing a large blood clot, was found in the midsuperior and posterior portion of

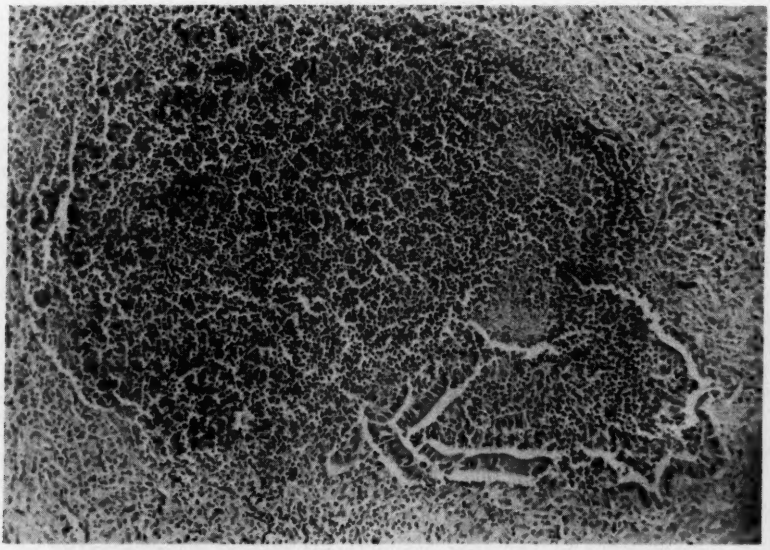


FIG. 2. One of many scattered microabscesses communicating with a biliary radicle which is also filled with purulent exudate. Hematoxylin and eosin stain, × 105.

the liver (Figure 1). It was flanked by two branches of the hepatic vein, and was in close proximity to radicles of the right hepatic bile duct. No arterial or venous source of the hemorrhage could be located in the wall of the cavity. The surrounding parenchyma was pale; the lobular pattern was accentuated. The biliary ducts in the vicinity of the lesion were enlarged and, when compressed, exuded blood and purulent material. The hepatic and portal veins contained no thrombi. Microscopic examination of hepatic tissue showed an acute generalized suppurative cholangitis which had produced scattered microabscesses (Figure 2). The architectural pattern of the liver was otherwise normal, and there was no evidence of chronic disease. Sections through the wall of the cavity showed it to be a hemorrhagic abscess (Figure 3). The wall was infiltrated with inflammatory cells; the area of necrosis extended into the surrounding parenchymal tissue. No evidence of cirrhosis, parasitic infestation, or of neoplastic or vascular lesions could be found grossly or microscopically.

The gall-bladder was greatly distended and completely filled with fresh red blood

(150 ml.). Its wall was thin and had a smooth outer surface; the serosal surface was granular and eroded. A small perforation was seen in the portion of the wall immediately adjacent to the abscess. The entire biliary ductal system was twice the normal size; the ducts contained quantities of fresh blood mixed with purulent exudate. The common bile duct measured 2.7 cm. in diameter (normal, 1.2 cm.); occasional areas of granulation were present on its mucosal surface. No obstructing lesions were found to account for the distention of the duct. No calculi were found in the gall-bladder or biliary ductal system, or in the fluid from the gastrointestinal tract. Microscopically, the wall of the gall-bladder contained areas of acute inflammation associated with tissue necrosis; no intramural hemorrhage was noted.

Approximately one-third of the pancreas was replaced by fatty tissue. No hemorrhagic foci were found, and the ducts communicating with the common bile

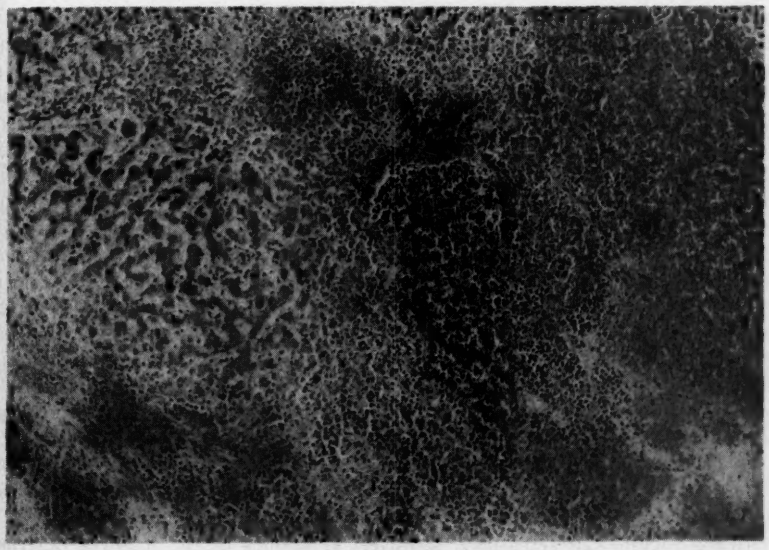


FIG. 3. Section of the wall of the large hematoma-abscess cavity. The blood-filled lumen of the abscess cavity is seen on the far right. The liver parenchyma on the left is atrophic and necrotic. Hematoxylin and eosin stain, × 105.

duct were patent. Microscopically, the pancreatic tissue showed scattered foci of fat necrosis and a slight infiltration of inflammatory cells.

The heart showed atherosclerotic changes and signs of a previous myocardial infarction, but no evidence of recent myocardial disease. Both kidneys were moderately nephrosclerotic. The adrenal glands appeared to be normal.

COMMENT

Sandblom, in his review of hemobilia consequent to central hepatic rupture,[4] noted that superficial lacerations of the liver, which affect only the small biliary ducts, rarely result in bleeding into the biliary duct system. In commenting on a case of hemobilia, cholecystitis, and gastrointestinal bleeding from rupture of the liver, Epstein and Lipshutz [7] pointed out the attendant dangers of bleeding,

particularly from the branches of the portal veins which are unable to effect any degree of hemostasis by spasm and which do not tend to collapse. In the case described in this report, post-mortem examination showed that the causative factor was acute hemorrhage from the wall of a large abscess deep in the hepatic parenchyma. The proximity of the abscess to the larger biliary radicles in the region of the portal fissure undoubtedly facilitated the drainage of blood into the biliary tree.

The post-mortem findings suggest the following sequence of events. The patient's recurrent abdominal pain before he was first hospitalized probably reflected an increasingly severe cholangitis. As the cholangitis progressed, intrahepatic microabscesses appeared, some of which coalesced to form one large hemorrhagic abscess. The massive gastrointestinal hemorrhage on the twelfth day of hospitalization apparently came from eroded sinusoidal vessels and small portal venous radicles in the wall of the large abscess. Despite their proximity to the abscess, the main hepatic veins had maintained their integrity, and no eroded arteries could be found by post-mortem dissection. Although the biliary tract, gall-bladder, and entire gastrointestinal tract contained large quantities of blood, no other source of hemorrhage could be found. The duodenal ulcer probably accounted for the hemorrhagic episode preceding the patient's first admission to a hospital in March, 1958, but it had healed by the time of subsequent bleeding. The liter of clotted blood in the peritoneal cavity presumably resulted from rupture of the gall-bladder shortly before the patient's death, since there was no evidence of peritoneal inflammation. There appeared to be no predisposing condition for the cholangiolitis. No calculi were found. No strictures were seen; the ampulla of Vater was widely patent. Whether hydroxycorticoid therapy played a role in the pathogenesis of the hemobilia is a matter for speculation. Because the lesion was not recognized as an abscess at the time of autopsy, no specimens of blood or exudate were taken for bacteriologic culture.

A diagnosis of hemobilia was not considered during the course of the patient's illness, but was established only after histologic examination of tissue removed post-mortem. The previous history of a duodenal ulcer undoubtedly was a confusing factor. In retrospect, however, a number of the features described by Sandblom as characteristic of "traumatic hemobilia" were demonstrated in this case. The "excruciating" abdominal pain which preceded the onset of gastrointestinal bleeding in our patient is common to all types of hemobilia, regardless of etiology or site of bleeding. Sparkman [12] attributed the characteristic colic of hemobilia, as well as the frequent occurrence of signs of extrahepatic obstructive jaundice, to obstruction of the common bile duct by blood clots. The occurrence of severe pain in the right upper quadrant of the abdomen, particularly if it is associated with hematemesis or melena, should suggest a diagnosis of hemobilia. Any abnormalities of liver function or a history of gall-bladder disease would strengthen this impression, especially if no blood dyscrasia or lesions of the gastrointestinal tract are demonstrable.

Summary

The case described in this report, although not diagnosed clinically, presented characteristic features of intrahepatic hemobilia, such as "excruciating" ab-

dominal pain preceding hematemesis and melena. On the basis of post-mortem findings, the fatal gastrointestinal hemorrhage was attributed to bleeding from eroded blood vessels in the wall of a large abscess deep in the hepatic parenchyma. This case, to our knowledge the first reported instance of biliary tract bleeding due to an abscess of the liver, emphasizes that hemobilia should be suspected whenever severe biliary colic is associated with unexplained gastrointestinal bleeding.

Acknowledgments

The authors are indebted to Dr. P. J. Sanazaro for his valuable assistance in the preparation of this article, and to Dr. P. Jensen, who performed the pathologic examination.

Summario in Interlingua

Le caso describite in le presente reporto, ben que non diagnosticate clinicamente, exhibiva certe aspectos characteristic de hemobilia intrahepatic, incluse intolerabile dolores abdominal sequite de hematemesis e melena. Super le base del constatationes necroptic, le mortal hemorrhagia gastrointestinal esseva attribuite al erosion de vasos de sanguine in le pariete de un grande abscesso profunde in le parenchyma hepatic. Iste caso, secundo nostre informationes le prime reportate exemplo de sanguination del vias biliari causate per un abscesso del hepate, sublinea le facto que hemobilia debe esser suspicite quandocunque sever colica biliari es associate con alteremente inexplicabile sanguination gastrointestinal.

BIBLIOGRAPHY

1. Lichtman, S. S.: Gastro-intestinal bleeding in disease of the liver and biliary tract. Amer. J. Dig. Dis. **3**: 439, 1936.
2. Kerr, H. H., Mensh, M., Gould, E. A.: Biliary tract hemorrhage: a source of massive gastrointestinal bleeding. Ann. Surg. **131**: 790, 1950.
3. Manfredi, D. H.: Gastrointestinal hemorrhage originating in the biliary tract. New York J. Med. **58**: 2397, 1958.
4. Sandblom, P.: Hemorrhage into the biliary tract following trauma; "traumatic hemobilia." Surgery **24**: 571, 1948.
5. Burnett, W. E., Rosemond, G. P., Caswell, H. T., Hall, J. H.: Unusual case of gastrointestinal hemorrhage. Surgery **26**: 1044, 1949.
6. Ekström, G., Hagberg, S.: Budd-Chiari's syndrome caused by haematoma of the liver; report of one case treated surgically. Acta chir. Scandinav. **112**: 107, 1957.
7. Epstein, H. J., Lipshutz, B.: Hemobilia, cholecystitis, and gastrointestinal bleeding with rupture of liver. J. A. M. A. **149**: 1132, 1952.
8. Francioli, P., Jost, A., Saegesser, F.: Hémobilie et syndrome de Chiari post-traumatiques. Helvet. chir. acta **21**: 465, 1954.
9. Hawthorne, H. R., Oaks, W. W., Neese, P. H.: Liver injuries with a case report of repeated hemorrhages through the biliary ducts. Surgery **9**: 358, 1941.
10. Menghetti, L.: Le emorragie epato-biliari (emobilie) di interesse chirurgico. Acta chir. ital. **13**: 971, 1957.
11. Sciacca, F.: Le rotture quasi spontanee del fegato. Policlinico (sez. chir.) **44**: 254, 1937.
12. Sparkman, R. S.: Massive hemobilia following traumatic rupture of the liver. Ann. Surg. **138**: 899, 1953.
13. Katzenstein, R., Ryan, A. J.: Rupture of liver with fatal hemorrhage due to intrahepatic vascular disease; report of 2 cases. J. A. M. A. **161**: 199, 1956.

14. Mackay, A. G., Page, H. G.: Hematemesis associated with hemobilia; report of a case due to an intrahepatic-artery aneurysm, with survival. New Engl. J. Med. **260**: 468, 1959.
15. Mast, W. H., Streamer, C. W.: Primary carcinoma of liver with spontaneous rupture, J. A. M. A. **100**: 1684, 1933.
16. Rudström, P.: Hemobilia in malignant tumours of the liver. Acta chir. Scandinav. **101**: 243, 1951.
17. Rolleston, H. D.: Diseases of the liver, gallbladder and bile ducts. 2nd Ed., 1912, Macmillan & Co., Ltd., London, p. 575.

HYDATID CYST OF THE LUNG WITH CLUBBING*

By Fouad A. Bashour, M.D., *Beirut, Lebanon*

Clubbing of the fingers and toes accompanies a variety of clinically unrelated diseases. It is present in certain pathologic conditions of the lung and pleura, in cyanotic heart disease, in subacute bacterial endocarditis, in sprue, in ulcerative colitis, in liver cirrhosis, and in myxedema following thyroidectomy.[1, 2] It may also be a familial characteristic transmitted as a Mendelian dominant.[3] With the advent of antibiotics, hypertrophic pulmonary arthropathy is most commonly associated with malignancy of the lung.[4]

In this paper, the rare association of hydatid cyst of the lung and digital clubbing is described. The mechanism of clubbing and the vascular changes that follow excision of the hydatid cyst are discussed. In 1,024 lung resections, clubbing was noted in 64 instances, and in only one instance was it associated with a hydatid cyst.[5]

Case Report

A 32-year-old male was admitted to the medical service of the American University of Beirut Hospital with the x-ray finding of a mass in the left lung. Four months prior to his admission an electric drill had accidentally struck his left chest. He developed bruises of the left axillary region, and complained of a vague left lower thoracic pain that increased on deep inspiration. A friction rub was heard at that time. A routine chest film revealed a globular mass in the left lung. The patient had no complaints of cough or expectoration.

On admission, the patient looked healthy and was in no acute distress. Blood pressure was 145/85 mm. of Hg. Pulse was regular. There was no lymph node enlargement in the neck or the axillae. There was some dullness to percussion in the left midaxillary region, coupled with decreased breath sounds and an inconstant friction rub. The heart was normal in size; no murmurs were heard. The second pulmonic sound was equal to the aortic second sound. The rest of the physical examination was essentially normal except for marked bilateral clubbing of the fingers and toes.

Laboratory study revealed normal urine. Hemoglobin (Sahli's method) was 17 gm. per 100 ml. The total leukocyte count was 6,000 per cu. mm., with 4%

* Received for publication September 17, 1959.
From the Cardiopulmonary Laboratory, American University of Beirut, Beirut, Lebanon.
Requests for reprints should be addressed to Fouad A. Bashour, M.D., Department of Internal Medicine, The University of Texas Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas 35, Texas.

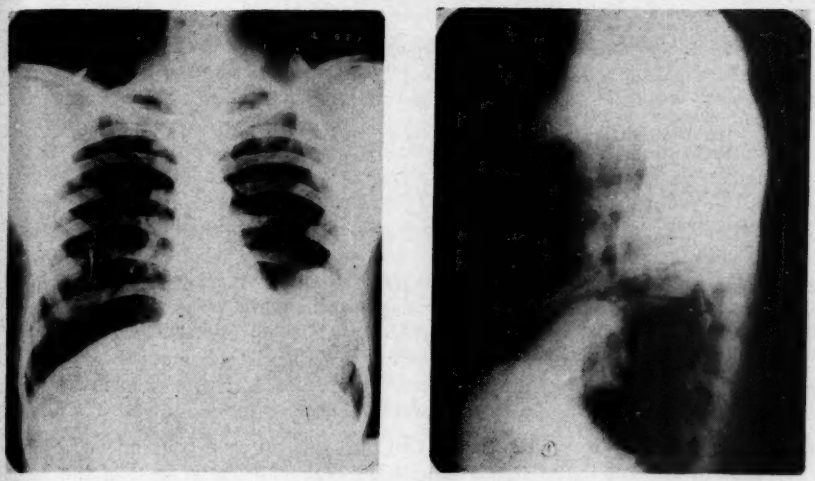


FIG. 1. A and B. Chest films (posteroanterior, left lateral), showing the hydatid cyst at the periphery of the left lung.

eosinophils in an otherwise normal differential count. The sedimentation rate was 4 mm. per hour. The platelet count was 296,000 per cu. mm. No immature neutrophils or normoblasts were found in the peripheral blood. The total serum proteins were 7.5 gm. per 100 ml., with 4.3 gm. albumin and 3.2 gm. globulins. The bromsulfalein retention was 5% in 45 minutes, and the alkaline phosphatase was 2.9 Bodansky units. Casoni's skin test was highly positive. The PPD (intermediate strength) skin test was negative. Weinberg's complement test was 1/8. Indirect hemagglutination test was negative.[6]

The electrocardiogram was normal. X-rays of the chest revealed a large cystic mass in the left lower lung above the diaphragm (Figures 1 A, B). Both diaphragms moved freely. The pulmonary function tests and the cardiac catheterization data are reported in Tables 1 and 2.

At operation, the cyst was superficially located in the left lower lobe. It measured 12 cm. in diameter, and contained 200 to 250 ml. of clear fluid. A culture of the hydatid fluid obtained at surgery was sterile. The diagnosis of hydatid cyst was confirmed by microscopy. The cyst wall consisted of a lamellar acellular membrane with a germinal layer and numerous scolices (Figure 2).

TABLE 1

Pulmonary Function Findings in this Patient as Compared with Those of a Normal Person

	Rate, min.	Tidal Air, ml.	Expiratory Reserve, ml.	Inspiratory Capacity, ml.	Vital Capacity, ml.	Alveolar Nitrogen, %	Functional Res. Capacity, ml.	Residual Volume, ml.	Total Lung Volume, ml.	Arterial CO_2 Content. mM./L.
Patient	12	600	450	3,600	4,050	2.3	2,500	2,050	5,900	22.48
Normal*	12	500	980 ±260	3,700 ±520	4,780 ±590	2.5	2,180 ±500	1,190 ±350	5,970 ±810	22

* Mean normal values from Kaltreider et al.[18] and Comroe et al.[19]

TABLE 2

Findings at Cardiac Catheterization

	Pressure mm. Hg	O_2 Saturation
Pulmonary artery	20/9	72
Right ventricle	24/1	—
Right atrium (mean)	3	71
Brachial artery	—	89–90*
Brachial artery after 100% O_2 inhalation	—	99

* Determined at different intervals.

Following surgery, a return of the oxygen saturation of blood samples from both the brachial artery and the cephalic vein to normal limits was observed, together with a decrease in the hemoglobin level (Table 3). There was no undue blood loss during surgery, the estimated amount being 200 ml.

DISCUSSION

Digital clubbing is a well known clinical sign. It is a consequence of hyperplasia of the soft tissue at the base of the nail with obliteration of the angle between the nail and the terminal phalanx. According to Bauer, it is a localized form of the general condition of hypertrophic pulmonary osteoarthropathy.[7] However, osteoarthropathy and clubbing may differ in several ways. Clubbing is commonly associated with a suppurative process, whereas osteoarthropathy is likely to be observed with a primary malignancy of the lung. Pain in pulmonary osteoarthropathy disappears shortly after the removal of the primary cause, but clubbing takes longer to regress.

The immediate cause of clubbing is not known. A number of theories have been proposed to explain its pathophysiology.[11] The association of gynecomastia and acromegaloid features in bronchogenic carcinoma with clubbing of the fingers has suggested the possibility of an endocrine imbalance.[4, 8] In three patients he studied, Ginsburg found that the urinary level of estrogen was

FIG. 2. Microscopic picture of the hydatid cyst wall.

elevated.[9] On the other hand, the increased frequency with which clubbing is observed in a peripherally located lung tumor favored the presence of a "pulmonary vascular reflex." The immediate cessation of pain in cases of hypertrophic pulmonary osteoarthropathy after vagotomy suggests that the vascular abnormality in the digits is mediated through efferent nerves from the lungs.[10] In unilateral clubbing due to an arteriovenous aneurysm, the rapid passage of blood distal to the lesion was reported to be essential to its formation.[11] Furthermore, neither of these mechanisms would explain the clubbing of an arteriovenous aneurysm. Mendlowitz [12] and Wilson [13] found increased blood flow in the clubbed fingers, and suggested a close relationship between clubbing and the increased blood flow. Increased vascularity and dilated vessels in the fingertips were found microscopically,[14] and were demonstrated by arteriography.[9]

In this patient, digital clubbing was secondary to the presence of the hydatid cyst in the left lung. A rise in the arteriovenous oxygen difference between the brachial artery and the cephalic vein after excision of the cyst would support this association (Table 2). In previously reported cases of bronchogenic carcinoma a small arteriovenous oxygen difference was found, and in one patient

TABLE 3

Blood Findings Before and After Surgery

	Brachial Artery		Cephalic Vein		A.V. O_2 Difference, %	Hemoglobin (Sahli), gm. %
	O_2 Content, vol. %	O_2 Saturation, %	O_2 Content, vol. %	O_2 Saturation, %		
Preoperative	20.30	89	19.51	85	4	20.5–17*
Postoperative	16.64	95	10.91	62	33	14.5

* Upper and lower levels as determined by Sahli's method.

the difference rose abruptly following surgery.[11] In a small group of patients in whom clubbing was caused by a variety of conditions, a small arteriovenous difference was found, suggesting vascular shunts in the fingertips.[16] A similar finding of a small arteriovenous oxygen difference was observed in cases of cirrhosis of the liver, with and without clubbed fingers.[17] The liver function tests performed in this patient were all within normal limits. There is no reason to assume that a hormone or a toxic or even an allergic substance was circulating in the blood.

In no previous instance of hydatid disease in the large series of cases collected at this hospital was clubbing present.[15] The indirect hemagglutination and Weinberg's tests specific for hydatid disease were both negative. The indirect hemagglutination test was positive in 49 of 50 cases of hydatid disease when the cyst was located in different organs of the body, including the lungs.[15] The location of the cyst at the periphery of the lung is consistent with the "reflex" theory, but is not necessarily the causative factor in clubbing.

The unsaturated arterial blood sample and the slight increase in its oxygen saturation after 100% oxygen inhalation for 10 minutes would suggest a large arteriovenous shunting in the lungs. The return of the oxygen content in the arterial blood sample to a normal level following surgery would seem to indicate

that these shunts were located in the vicinity of the cyst. The restricted expiratory reserve associated with an increase in the residual volume is probably the result of the patient's inability to ventilate adequately those alveoli in the vicinity of the cyst. Unfortunately, these tests were not repeated after the removal of the hydatid cyst.

Summary

An adult patient with hydatid cyst of the left lung and clubbed fingers and toes was reported. A number of mechanisms might be responsible for the formation of clubbing. In this patient the location of the cyst at the periphery of the left lung was suggestive of a possible relationship between the presence of clubbing and the so-called "pulmonary vascular" reflex. Blood shunting across the hands and in the lungs was observed. The peripheral arteriovenous oxygen difference returned to the normal level following removal of the lung cyst.

Summario in Interlingua

Esseva studiate un patiente adulte con un cyste hydatic del pulmon e digitos hippocratic del manos e pedes. Le sito del cyste esseva peripheric in le pulmon sinistre. Un ruito de friction esseva audibile supra le area del cyste.

Ante le operation, un specimen de sanguine ab le arteria brachial esseva dissaturate. Post 10 minutas de respiration de 100% de oxygeno, le saturation arterial de oxygeno montava a 99%. In le vasculatura peripheric un micre differentia del saturation oxygenic esseva observate inter specimens de sanguine obtenite ab le arteria brachial e le vena cephalic. Iste constatationes suggere le presentia de un derivation dextero-sinistre intrapulmonar e un derivation arteriovenose in le mano. Iste derivationes regredeva post le ablation del cyste.

Le presentia de digitos hippocratic in iste patiente esseva relationate in un maniera o un altere con le presentia del cyste hydatic. Le sito del cyste al peripheria del pulmon es congruente con le "theoria reflexe." Tamen, il es possibile que le derivationes pulmonar es le causa fundamental del digitos hippocratic.

BIBLIOGRAPHY

1. Mendlowitz, M.: Digital circulation. Grune and Stratton, New York, 1954.
2. Editorial: Clubbing of fingers. Brit. Med. J. **1**: 778, 1955.
3. Seaton, D.: Familial clubbing of the fingers and toes. Brit. Med. J. **1**: 614, 1938.
4. Hammarsten, J., O'Leary, J.: The features and significance of hypertrophic osteoarthropathy. Arch. Intern. Med. **99**: 431, 1957.
5. Wierman, W., Clagett, T., McDonald, J.: Articular manifestations in pulmonary diseases. J. A. M. A. **155**: 1459, 1954.
6. Garabedian, G., Matossian, R., Djanian, A.: An indirect hemagglutination test for hydatid disease. J. Immun. **78**: 269, 1957.
7. Bauer, W.: Diseases of the bones, *in* Cecil, R. L., Loeb, R. F.: Textbook of medicine, 8th Ed., W. B. Saunders Company, Philadelphia, p. 1345, 1951.
8. Biwas, S.: Generalized hypertrophic osteoarthropathy with gynecomastia. J. Indian Med. Ass. **25**: 326, 1955.
9. Ginsburg, J.: Observations on the peripheral circulation in hypertrophic pulmonary osteoarthropathy. Quart. J. Med. **27**: 335, 1958.
10. Flavell, G.: Reversal of pulmonary hypertrophic osteoarthropathy by vagotomy. Lancet **1**: 260, 1956.

11. Semple, T., McCluskie, R.: Generalized hypertrophic osteoarthropathy in association with bronchial carcinoma. Brit. Med. J. 1: 754, 1955.
12. Mendlowitz, M.: Clubbing and hypertrophic osteoarthropathy. Medicine 21: 269, 1942.
13. Wilson, G.: Local circulatory changes associated with clubbing of the fingers and toes. Quart. J. Med. 12: 201, 1952.
14. Lovell, R.: Observations on the nature of clubbed fingers. Clin. Sci. 9: 299, 1950.
15. Jidejian, Y.: Personal communication.
16. Bashour, F.: Arteriovenous oxygen difference in clubbed fingers. To be published.
17. Silverstein, E.: Peripheral venous oxygen saturation in patients with or without liver disease. J. Lab. Clin. Med. 47: 513, 1956.
18. Kaltreider, N., Fray, W., Van Zile Hyde, H.: The effect of age on the total pulmonary capacity and its subdivisions. Amer. Rev. Tuberc. 37: 662, 1938.
19. Comroe, J. H., Forster, R. E., Dubois, A. B., Briscoe, W. A., Carlsen, E.: The lung—clinical physiology and pulmonary function test. The Year Book Publishers, Inc., Chicago, 1955.

CHRONIC FAMILIAL GIANT URTICARIA *

By Jack D. Cohen, M.D., F.A.C.P., *Boston, Massachusetts*

Since 1888, when Osler recorded in detail the first full description of "hereditary angioneurotic edema," our knowledge of this baffling illness has advanced very little, if at all. The purpose of this paper is threefold: first, to add another family tree to the literature, which now embraces about 40 family histories; second, to familiarize the physician with unusual aspects of this form of urticaria, and to assess therapy now available; third, to show why this disease should be considered as nonallergic.

We feel that "angioneurotic" is a poor term, especially with regard to the familial variety of this disease, and it will not be used further in this paper. In the reported cases, emotional or nervous factors bear little if any causal relationship to attacks. The nervous system rarely does—but may—act as a trigger mechanism to release an abnormal physiologic process, controlled by heredity. This is an illness, hereditary in nature, probably transmitted as a Mendelian dominant. It can be transmitted by those who are not affected. It usually develops in late childhood, but may develop at any time from infancy to adulthood. Once the illness appears, it tends to recur throughout the patient's lifetime, although it may be less frequent in the later years. Skin tests are negative or falsely positive. There is no eosinophilia, and laboratory data, with the possible exception of protein studies, are entirely normal. The attacks come on periodically, often as frequently as every two weeks, throughout life. The edema can occur in any organ, even the brain, but the usual case is characterized by giant cutaneous urticaria, with gastrointestinal involvement second in order of frequency. Pharyngeal and laryngeal edema is common, the laryngeal form being the chief cause of death. The mortality rate is high. In 35 families reported up to 1940,[8] 28% of the members died from edema of the

* Received for publication September 21, 1959.
Requests for reprints should be addressed to Jack D. Cohen, M.D., 47 Bay State Road, Boston 15, Massachusetts.

larynx. In the Crowders' [5] case report of five generations, of which 28 members had the disease, there were 15 deaths. In Dunlap's [7] case report of 24 members who had the disease in four generations, there were six sudden deaths, at least four of which were due to laryngeal or gastrointestinal edema. The pre-epinephrine era death rate was about 21%. Since then it has been lower, but is still substantial. In the present report of 25 patients with the disease, there have been two deaths from laryngeal edema, and one following surgery for gastrointestinal edema. Reports of mortality vary from 7% to 50%. Epinephrine lowers the mortality, but it may fail to be effective.

Gastrointestinal edema is very common, and affects the majority. Osler gave an excellent description of the attacks of nausea, vomiting, and severe colic associated with it. Distention is usually present. It is important to avoid unnecessary surgery, as there is a high mortality rate under these circumstances. The case reported below will enlarge on this aspect. At operation, one finds edema involving the mucosa, submucosa, and muscle, and, in some, pinkish fluid in the peritoneal cavity. Biering [14] x-rayed a patient during an attack and found

TABLE 1

	Total Protein	Albumin	Globulin	$Alpha_1$	$Alpha_2$	Beta	Gamma
During Attack	6.5	3.92	2.58	0.22	0.54	0.64	1.18
Free Period	6.1	3.86	2.25	0.21	0.42	0.68	0.94
Normal Range	6–8	3.5–4.5	2.5–3.5	0.3–0.5	0.5–0.7	0.8–1.0	0.8–1.2

a pattern of ileus with gas-filled spaces and fluid levels. Another had gastric retention and invagination in the ascending colon. The white count in gastrointestinal attacks may vary from 16,000 to 20,000. There is no eosinophilia.

Insofar as treatment is concerned, there is none of value to date with the exception of epinephrine, and this often does no good. ACTH and cortisone have been used without avail,[13] and may be harmful. Antihistamines also are of no value.[12]

As stated above, all laboratory data, including blood chemistry, have been normal in patients with this illness. Fineman,[9] however, studied plasma proteins and found that the A/G ratio rose during an attack while the total protein remained constant. In other words, the globulin would fall during an attack and rise during the asymptomatic period, the albumin doing the opposite. This finding was not substantiated in the present case, however. The total protein and fractional values are given in Table 1. The small differences are within laboratory error and are not clinically significant.

CASE REPORT

A 39-year-old woman developed giant urticaria at the age of eight and has had attacks about every two weeks since. The attacks affect the skin, usually on the face, hands, feet, or genitalia. There is almost always gastrointestinal involvement, which varies in severity. The attacks are characterized by severe abdominal colic, nausea, vomiting, distention, abdominal tenderness and, at times, mild diarrhea. At the age of 14 the patient had an appendectomy, which followed a diagnosis that was

incorrect, since she had been having an attack of urticaria. Three years ago there was a period of freedom from gastrointestinal involvement which lasted for six months. The longest term without any cutaneous attack has been one month. The patient believes the attacks are mildly related to infection and fatigue, but states that they are just as frequent on vacations. Emotional upset seemed to bring on an attack on only two occasions; one of these was the death of her mother, the other a false accusation by a fellow worker.

Attacks show no apparent relation to the patient's menses, or to the ingestion of alcohol or food. Skin tests on two occasions gave negative results. Many of the attacks are associated with erythema multiforme, characterized by serpiginous erythematous welts, chiefly on the face. (This correlation has been noted by MacKenzie.[10]) The only medication which has had any value is epinephrine, especially for the edema of the pharynx and larynx. On two occasions, hospitalization was necessary, as tracheotomy was being considered for the laryngeal involvement. For the gastro-

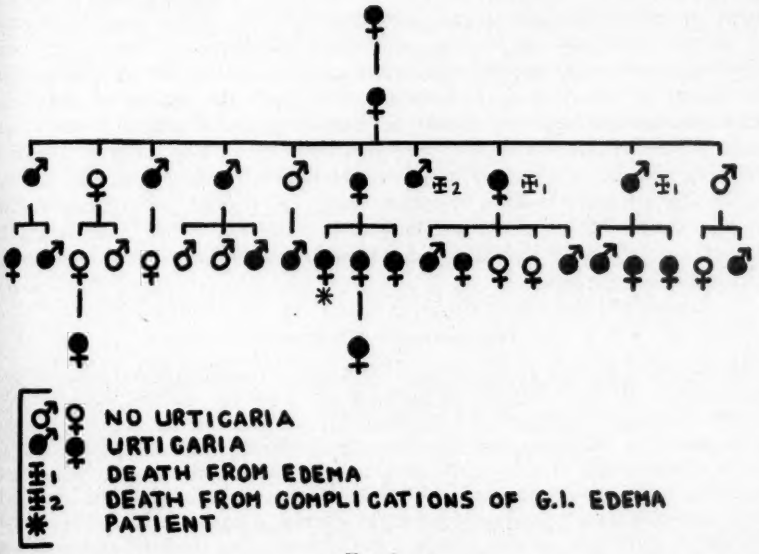


FIG. 1.

intestinal attacks, Demerol gives temporary relief while one waits 36 to 48 hours for natural subsidence of the attack to occur. Many antihistamines have been used, as well as Atarax, phenothiazine, histamine "desensitization" by intradermal injections, elimination diets, change in intestinal flora with *Bacillus acidophilus,* and large doses of vitamin C, vitamin B_{12}, and flavonoids. None of the above measures have been of any value.

The family tree of our patient is illustrated in Figure 1. Of 36 persons in five generations, there have been 25 with attacks of urticaria. Twelve have had appendectomies for what was found to be "normal appendix" (i.e., gastrointestinal urticaria). There have been three deaths due to urticaria, two due to laryngeal involvement and one due to complications following gastrointestinal surgery for visceral edema which caused obstruction.

The patient's mother died of cancer of the uterus, but she had had visceral and

cutaneous urticaria from childhood. Her grandmother, the "source" as far as can be determined, is now 95 and has had the same involvement. The patient has five uncles living, only one free of the disease. However, one of his children has a mild course (two attacks to date). Six members of the family have seen psychiatrists, without benefit. One uncle received cortisone, which made him much worse. For this reason, steroids were not used on this patient.

Summary

A case report and a family history of familial giant urticaria are described. In five generations of 36 persons, there have been 25 with urticaria, and three deaths, two from laryngeal edema, and one postsurgically, from gastrointestinal edema. There have been 12 appendectomies because of incorrect diagnoses.

The patient illustrates the failure of all types of medication presently available. Epinephrine occasionally helps. Demerol or morphine should be used as needed for relief of the pain in gastrointestinal attacks. There is no evidence of any allergic basis for this disease, and there has been no response to such anti-allergic drugs as steroids and antihistamines. There is no eosinophilia. The disease is inherited as a dominant trait, with the nature of the defect presently undetermined. It should be considered as a separate entity, and should not be grouped with acquired giant urticaria. The latter responds to anti-allergic medication of various types; the familial variety does not. It is a serious disease, with a high mortality rate. A patient with familial giant urticaria should be aware of its dangers and alerted to the indications for tracheotomy. Also, he should be taught the self-administration of epinephrine, which may be life saving.

Summario in Interlingua

Es reportate un caso de chronic gigante urticaria familial que interessava cinque generationes. Un total de 25 ex 36 personas esseva afficite, con tres mortes. Deceduo del subjectos esseva operate pro appendicitis super le base de diagnoses erronee. Le frequentia de affectiones gastrointestinal es illustrate. Le autor opina que iste typo de urticaria non es de origine allergic sed resulta de un non-cognoscite factor que es transmittite como character dominante. Il non ha eosinophilia in iste morbo. Omne medicationes anti-allergic remane sin effecto in casos del varietate familial. Demerol o morphina es de grande valor durante le attaccos gastrointestinal. Adrenalina pote sed non debe esser de adjuta in le tractamento de edema laryngee, sed tracheotomia es a vices indispensabile e apte a salvar le vita del patiente. Patientes con iste morbo debe esser informate del periculo de illo. Illes debe esser instruite in le auto-administration de adrenalina e con respecto al indicationes pro tracheotomia.

BIBLIOGRAPHY

1. Osler, W.: Hereditary angioneurotic edema. Amer. J. Med. Sci. **95**: 362, 1888.
2. Griffith, T. W.: Remarks on a case of hereditary localized edema proving fatal by laryngeal obstruction. Brit. Med. J. **1**: 1470, 1902.
3. (a) Morris, R. S.: Final note on case II of angioneurotic edema. Amer. J. Med. Sci. **130**: 382, 1905.
3. (b) Morris, R. S.: Angioneurotic oedema: report of two cases with the histology of a portion of the gastric mucosa obtained by the stomach-tube. Amer. J. Med. Sci. **128**: 812, 1904.

4. Fairbanks, A. F.: Hereditary oedema. Amer. J. M. Sci. **127**: 877, 1904.
5. Crowder, J. R., Crowder, T. R.: Five generations of angioneurotic edema. Arch. Intern. Med. **20**: 840, 1917.
6. Wason, I. M.: Angioneurotic edema, report of case with necropsy findings. J. A. M. A. **86**: 1332, 1926.
7. Dunlap, H. F., Lemon, W. S.: The hereditary type of angioneurotic edema. Amer. J. Med. Sci. **177**: 259, 1929.
8. Longcope, W. T., Winkenwerder, W. L.: Anaphylaxis, serum disease, urticaria, and angioneurotic edema, *in* Nelson new loose-leaf medicine, Vol. 2, T. Nelson & Sons, New York, p. 647, 1951.
9. Fineman, A. H.:Hereditary angioneurotic edema. Ann. Intern. Med. **14**: 916, 1940.
10. MacKenzie, G. M.: Angioneurotic edema, *in* Cecil, R. L.: Textbook of medicine, 7th Ed., W. B. Saunders Company, Philadelphia, pp. 550–551, 1948.
11. Barnet, A. F.: Hereditary angioneurotic edema. A remarkable family history. Calif. Med. **69**: 376, 1948.
12. Sheldon, J. M., Schreiber, E. O., Lovell, R. G.: Hereditary angioneurotic edema with a case report. J. Lab. Clin. Med. **34**: 524, 1949.
13. Spaulding, W. B.: Hereditary edema in 2 families. Canad. Med. Ass. J. **73**: 181–187, 1955.
14. Biering, A.: Abdominal pains in edema. Acta med. Scandinav. **153**: 373–382, 1956.

SYMMETRIC PERIPHERAL GANGRENE IN PNEUMOCOCCAL SEPSIS *

By Richard E. Bettigole, M.D., *Oklahoma City, Oklahoma*

The unexpected appearance of symmetric peripheral gangrene in a patient under treatment for pneumococcal pneumonia, bacteremia, and meningitis has led to a consideration of the many likely causes of this condition, and the possible means of avoiding or alleviating it.

Case Report

A 60-year-old former cook and mental hospital inmate was first seen at the University of Oklahoma Medical Center in the Medical Clinic on February 24, 1959, with a chief complaint of pain in the chest and in the left upper quadrant since an automobile accident on December 1, 1958. He had had an exploratory laparotomy several days after this accident, at which time clotted blood was found in the peritoneal cavity. Past history included deferment from the armed services in 1918 for a "bad lung," a chancre in 1919, gonorrhea in 1921, brain concussion and a possible skull fracture in 1937, followed by 28 days of unconsciousness, and an appendectomy in 1946. There was a history of epistaxis for about one year, easily controlled by pressure, and also of a moderate chronic cough productive of brownish, occasionally blood-streaked sputum. The patient complained also of frequency, urgency, and nocturia. Physical examination showed marked clubbing of the fingers and slight

* Received for publication September 1, 1959.
From the Department of Medicine, University of Oklahoma Hospitals, Oklahoma City, Oklahoma.
Requests for reprints should be addressed to Richard E. Bettigole, M.D., Department of Medicine, University of Oklahoma Hospitals, 800 Northeast Thirteenth Street, Oklahoma City 4, Oklahoma.

cyanosis. The blood pressure was 170/100 mm. of Hg. Breath sounds were diminished, and the patient complained of moderate chest pain on deep breathing or on percussion anywhere on his chest.

Laboratory examinations included a negative urinalysis; blood urea nitrogen, 8 mg.%; hemoglobin, 13.8 gm.%; white blood cell count, 10,450 per cubic millimeter; neutrophils, 61%; lymphocytes, 25%; eosinophils, 5%; monocytes, 9%. Total serum protein was 7.7 gm.%, with an albumin of 4.6 gm.%. Cephalin flocculation was 2-plus in 48 hours. The result of the serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was reactive; Kolmer's test, 1-plus. On March 12, 1959, the patient returned to the medical outpatient clinic, and at that time x-rays showed compression fractures of the fifth and ninth thoracic vetebrae, and moderate fibrosis at both lung bases. The patient complained of increased productive cough and a four-pound weight loss between visits. He was started on 1 gm. tetracycline daily, which he took for 10 days, until the day before admission. On March 19, 1959, the patient again returned to the clinic, complaining of epistaxis, and it was noted that his social situation was such that he was getting only one meal per day, which was thought to account at least in part for his weight loss. On the evening of March 23, 1959, the patient was sent, unaccompanied, to the University of Oklahoma Hospitals from the emergency room of a nearby hospital; he was semicomatose and was able to give no details of his illness.

History obtained after the patient's sensorium cleared several days later revealed that he had been "frostbitten" in 1921, and had noted thereafter that his hands at times became cold and blue on exposure to low temperatures; no particular changes in the face had ever been noted. The patient had spent the years from 1937 to 1958 in a state mental hospital, the first 17 of these years having been spent in an "acute" ward. He apparently had been accused of attempting to rape an eight-year-old girl at some time prior to his admission to the mental hospital, and it may be that this was what precipitated his being committed there. During the 21 years of custodial care he had received a total of only three visitors. On discharge it was thought that he was not psychotic, and very likely never had been. Until admission to the University of Oklahoma Hospitals the patient had been living at a mission society in Oklahoma City, where he did light janitorial work in exchange for a bed and one meal a day.

Physical Examination: Temperature, 103.8° F. rectally; pulse, 120 per minute and regular; respirations, 20 per minute; blood pressure, 110/65 mm. Hg. The patient was a dirty, emaciated, odorous old man, answering "Yes, ma'am" to all questions. He lay flat in bed with his neck extended, resisting attempts to flex his neck. He was very markedly dehydrated and cyanotic, and it was noted that the cyanosis in his toes appeared to be somewhat less than that in his fingers and in the circumoral area. The head showed no evidence of trauma. Funduscopic examination showed only moderate arteriolar tortuosity. The tongue and oral pharynx were coated with thick, yellow mucus. The chest had a slightly increased anteroposterior diameter, and examination of the lungs revealed decreased breath sounds, but no other abnormalities to percussion or auscultation. There appeared to be bilateral costovertebral angle tenderness. Rectal examination revealed poor sphincter tone, and the stool was watery, light tan, and mucoid in appearance. Marked clubbing of the fingers and toes was noted, but no peripheral edema. Deep tendon reflexes were equal and active; the patient moved all his extremities, but sensory examination was unsatisfactory.

Laboratory: Hemoglobin, 15 gm.%; hematocrit, 46%; white blood cell count, 29,850 per cubic millimeter; polymorphonuclear leukocytes, 98% (with 28% bands); lymphocytes, 2%. Urinalysis showed a specific gravity of 1.020, pH of 5, 1-plus albumin, negative sugar, and 3 to 5 white blood cells per high power field. Blood

urea nitrogen, 84 mg.%; fasting blood sugar, 96 mg.%. Lumbar puncture revealed clear fluid, with an opening pressure of 70 mm. of spinal fluid and a closing pressure of less than 20 mm. of spinal fluid; 22 cells per cubic millimeter, of which 20 were erythrocytes and the other two lymphocytes; protein, 35 mg.%. Chest x-ray showed diffusely increased markings at the right base.

Hospital Course: The patient was given intravenous fluids and intravenous penicillin therapy on the night of admission on the basis of a presumptive diagnosis of bronchopneumonia, probably with septicemia. Sinus and mastoid films were negative. The next morning, two blood cultures which were taken shortly after admission and the spinal fluid culture were reported as containing gram-positive diplococci, which subsequently proved to be *Diplococcus pneumoniae*. Therapy with intravenous penicillin was continued for a total of 94,000,000 units of aqueous penicillin over the first seven hospital days.

By the evening of the day following admission the temperature was 100.4° F. rectally, the pulse, 90 per minute. The patient was comatose, and lay with his neck extended and his eyes rolled up and to the right. Intense cyanosis of the hands and of the perioral region was present even after insertion of a nasal oxygen catheter, but there was only slight cyanosis of the toes. The following morning the patient appeared to be more alert, and the cyanosis appeared to be slightly less marked; the temperature was 99.8° F. rectally. Spinal tap on this day (the third hospital day) showed 1,000 white cells per cubic millimeter, of which 98% were polymorphonuclear leukocytes. The protein was 200 mg.%, and a gram stain of the spinal fluid showed gram-positive diplococci, but culture of this specimen was negative. That afternoon it was noted for the first time that the patient's cyanosis appeared to be patchy, no longer affecting the right thumb or forefinger or any of the circumoral area except for a 4 by 5 cm. area of the upper lip; a 1 by 2 cm. area of the left cheek; and a ½ by ½ cm. area at the bottom of the left earlobe, which also showed blue-black skin. The blood urea nitrogen was 26 mg.% on this day, but the white count was still 30,000, with 92% polymorphonuclear leukocytes, and a marked shift to the left. At 7:00 p.m. it was noted that there was a definite area of blackish skin over the bridge of the nose as well as on the portions of the upper lip, left cheek, and left earlobe described above. In the right hand only the "pad" of the distal phalanx of the fifth finger was still affected, but it was definitely black. The left third, fourth, and fifth fingers were cool and bluish black in color, and this discoloration, which a little earlier had extended approximately from the phalangeal-metacarpal joints distally, now affected only the distal phalanges, being worse in the third and fifth fingers than in the fourth. Radial and ulnar pulses were full, and it was noted that there was very definite hyperemia of the hands and wrists just above the cyanotic areas.

It was felt that, in view of the hyperemia noted, the patient had as much vasodilation about the affected areas as his vessels were capable of. Vasodilator drugs were not used for fear of throwing him into systemic shock or decreasing the circulation in affected areas. Stellate ganglion and brachial plexus blocks were discussed, but it was felt that, in a patient who was unable to cooperate, the risk of intravascular injection of the local anesthetic or of inducing a pneumothorax was too great in the face of the uncertain benefits that might result from a successful block.

The patient gradually improved, remaining almost afebrile, and becoming quite alert by the fifth hospital day, when the accompanying photographs were made (Figures 1 and 2). The gangrenous areas of tips of the third, fourth and fifth fingers on the left hand and of the fifth finger on the right hand became black, hard, and shrunken. The gangrenous skin over the nose proved to be a superficial lesion and soon peeled off spontaneously, as did the lesions on the left cheek and left earlobe. There was minor sloughing of the affected area of the upper lip, but it continued to heal well with local treatment. Further studies were done, with the results noted:

vital capacity, 2.8 L.; arterial oxygen saturation, 91.6%; cryoglobulins negative; Sia water test, negative; typhoid, paratyphoid, brucella, and proteus OX19 agglutinins, negative; serum sodium, potassium, chlorides, and CO_2, normal; bromsulfalein excretion, normal. The leukocyte count had returned to normal by two weeks after admission. Three L.E. cell preparations were negative. The seven days of intravenous penicillin therapy were followed by intramuscular procaine penicillin therapy for 10 days. Lumbar puncture on the twelfth hospital day showed only three lymphocytes and a protein of 42 mg.%, and culture was negative. The patient received two bilateral stellate ganglion blocks approximately two weeks after the onset of the

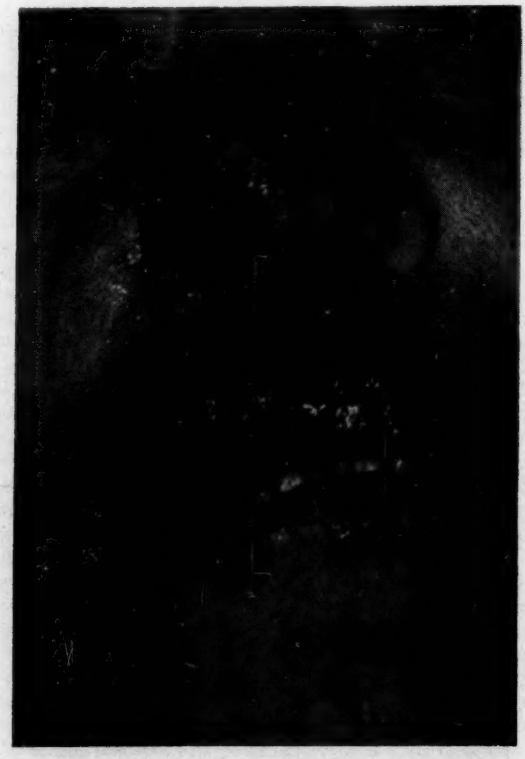


FIG. 1. Gangrene of the nose and lip on the fifth hospital day.

gangrene, without any symptomatic improvement in the burning pain in his fingers. He was also treated with sublingual nitroglycerin and with buccal streptokinase-streptodornase, without any objective or subjective improvement. He was given norepinephrine by vaporizer four times daily for two days, with a Bennett positive-pressure machine for his presumed chronic bronchitis; this produced no improvement in the slight cough which he occasionally had, but did produce some increased burning pain in his fingers, and possibly some slight progression of the vascular lesions. By the twenty-sixth hospital day it was evident that the lip and nose were healing well, but the condition of the hands remained static, and burning pain continued to trouble

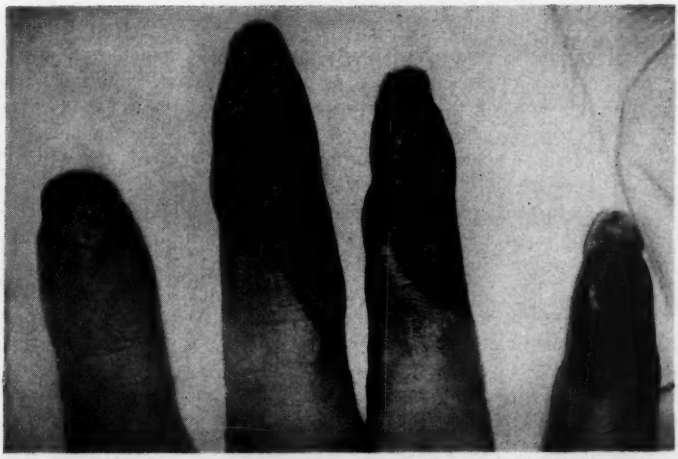


FIG. 2. The gangrenous fingers of the left hand on the fifth hospital day.

him considerably. On the thirty-sixth hospital day the gangrenous fingertips were amputated, and after an initial postoperative temperature elevation to 101° F. the patient did very well, noting great diminution in and then disappearance of the burning pain in his fingers. Microscopic examination of the amputated fingertips showed extensive necrosis of the tissues, with some intimal thickening of the small vessels. No evidence of thrombosis was found. Gastrocnemius muscle biopsy showed no evidence of collagen disease. The patient was discharged from the hospital on May 8, 1959, with the digital amputations apparently healing well. Follow-up examination four weeks later showed good healing at the amputation sites.

FIG. 3. General appearance on the fifth hospital day.

Discussion

Peripheral gangrene occurring in the course of systemic disease has been reported in a variety of illnesses. Cases are reported in which the gangrene complicated circulatory collapse due to myocardial infarction,[1, 2] congestive heart failure,[3, 4] paroxysmal ventricular tachycardia (in a case of myocardial gumma),[5] "ball thrombi" of the left atrium occluding the mitral valve,[6] overwhelming infections such as cholera,[7, 8] pneumonia,[9] and meningococcemia.[10, 11] On the other hand, no peripheral gangrene was noted in 43 patients with shock caused by bacteremia due to gram-negative bacilli.[12] Gangrene of the nose simulating "angiospastic" gangrene has been reported, with embolization from bacterial endocarditis.[13, 14] Other well known causes of peripheral gangrene, and more specifically of symmetric peripheral gangrene, include Raynaud's disease, vascular obliteration by arteriosclerosis obliterans or "collagen disease," cold injury, and ergot poisoning.

A few cases of peripheral gangrene occurring in pneumonias without obvious circulatory collapse have been reported. Storstein reported a case of symmetric peripheral gangrene complicating pneumonia (organism unknown), with autopsy findings including a thrombus in a digital artery which showed incipient organization.[15] Uhr grew type 4 pneumococci from the blood and from the exudate from a gangrenous toe in a case of pneumonia in a nine-year-old boy who developed bilateral gangrene of the great toes and who survived after treatment with sulfanilámide.[16]

In the present case, a number of factors were present which can be incriminated in the development of gangrene. The patient had a history of previous cold injury, and Raynaud's phenomenon occurred when he was subsequently exposed to cold. He was extremely dehydrated on admission, with a consequent relative polycythemia, and there may have been an element of shock, in that his blood pressure was 110/65 mm. of Hg, compared to previous slightly hypertensive readings. He was also said to have been exposed to cold rain three days before admission, and to have slept in his wet clothes.

In a consideration of the etiology of the gangrene in this case, it is difficult to choose among the different possibilities that present themselves. The apparent rarity of this complication leads one to speculate that perhaps peripheral gangrene is produced only by a fortuitous combination of predisposing factors. Certainly shock and dehydration may complicate severe bacterial infections, but this patient was never actually in clinical shock, unless it was before he was brought to the hospital. On the other hand, similar cold injuries have been described, especially during wartime, and sequelae such as this do not appear to have been noted.

Once gangrene develops, with hyperemia of surrounding areas, it is difficult to predict favorable results from treatment either with vasodilation or with anticoagulants. Vasodilation by the use of systemic or local intra-arterial medication, or with sympathetic nerve blocks, runs the risk of producing a relative fall in the blood flow in the affected parts. Since the vessels surrounding the gangrenous areas may already be maximally dilated, all one may achieve is dilation of the vascular bed in uninvolved areas, and a consequent loss of circulation in the involved areas. Use of anticoagulants incurs the usual risks of this mode of therapy, and may seem questionable in the face of an established but

nonprogressive lesion. Certainly the most important rule in the therapy of such peripheral gangrene is to avoid lessening the circulation in the involved areas with constricting clothing about the extremities, tight restraints, vasoconstrictor drugs (such as were used briefly in this case), or exposure to cold.

This complication is so rare that it would be very difficult to assess the results of attempts to avoid it. It might be suggested, however, that if an individual with a history of cold injury becomes ill with an acute systemic bacterial infection, special efforts be made to avoid exposure to cold and prolonged tourniquet-like constriction of any extremity, to avoid or cut short septicemic shock without the use of pressor amines (by use of intravenous adrenal cortical steroids along with "massive" antibiotic therapy), and possibly to give anticoagulants such as heparin at the very first sign of incipient gangrene.

Summary

A case of symmetric peripheral gangrene complicating pneumococcal pneumonia and meningitis is presented, and the theory is proposed that this phenomenon may be due to a fortuitous combination of many predisposing factors, including extreme dehydration and previous cold injury. Possible means of attempting to avoid this condition and of treating it are discussed.

Summario in Interlingua

Un masculo de racia blanc de 60 annos de etate disveloppava pneumonia pneumococcal, meningitis, e bacteremia. Plure dies post le declaration del morbo, gangrena sic se faceva evidente in plures del punctas de digito in ambe manos, in un portion del labio superior, e in le pelle coperiente le puncta del naso, le eminentias malar, e le lobos de aure. Le patiente se restabliva ab iste infection post un intense tractamento con penicillina. Le afficite punctas de digito se curava ben post amputation proxime al linea de demarcation. Le altere lesiones esseva multo superficial e se restaurava sin intervention chirurgic.

Es notate previe reportos de gangrena symmetrico-peripheric associate con collapso circulatori in consequentia de varie typos de morbo cardiac o de massive infectiones. Embolismo ab endocarditis bacterial es etiam capace a producer un simile tableau clinic, e le mesmo vale pro morbo de Raynaud, oblitteration vascular per arteriosclerosis oblitterante o "morbo de collageno," vulneration per frigido, e invenenamento ergotic. Tamen, le complication de gangrena es rar, in despecto del relativemente plus grande frequentia de plures del conditiones predisponente, e il es de interesse notar que nulle caso es reportate in un serie de 43 patientes con choc per bacteremia causate per bacillos negative al gram.

Es conjecturate que le gangrena peripheric in nostre patiente esseva le resultato de un pluralitate de factores predisponente: Un previe vulneration per frigido (perniones in 1921), recente exposition a frigido, dishydratation, hypotension, e le presentia physic in le sanguine de grande numeros de bacterios. Ab le puncto de vista del tractamento, il pare que il habeva occurrite un grado maximal de vasodilatation in le tissus adjacente al areas de ischemia, de maniera que un tractamento systemic con drogas vasodilatatori o con blocos de plexo brachial o de ganglion stellate haberea, probabilemente, reducite plus tosto que augmentate le fluxo de sanguine ubi illo esseva requirite le plus urgentemente. Anticoagulation rapide esseva prendite sub consideration quando le ischemia primo comenciava disveloppar se, sed il esseva determinate non usar iste forma de therapia.

In subjectos con un historia de vulneration per frigido o de phenomeno de Raynaud, le disveloppamento de un acute infection systemic indica que omne effortio debe esser facite pro evitar exposition a frigido, constriction del extremitates, dishydratation, e—evidentemente—hypotension.

BIBLIOGRAPHY

1. Swan, W. G. A., Henderson, C. B.: Peripheral gangrene in myocardial infarction. Brit. Heart J. **13**: 68, 1951.
2. Caserta, S. J., Metz, R., Anton, M.: Symmetrical peripheral gangrene in myocardial infarction; report of a case. New Engl. J. Med. **254**: 568, 1956.
3. Bird, T., Leithead, C. S., Lowe, K. G.: Symmetrical peripheral gangrene in low-output heart failure. Lancet **2**: 780, 1954.
4. Perry, C. B., Davie, T. B.: Symmetrical peripheral gangrene in cardiac failure. Brit. Med. J. **1**: 15, 1939.
5. Abrahams, D. G.: Incipient symmetrical peripheral gangrene complicating paroxysmal tachycardia. Brit. Heart J. **10**: 191, 1948.
6. Abramson, J. L.: Ball thrombi of the heart. Ann. Clin. Med. **3**: 327, 1924.
7. Rogers, L.: Cholera and its treatment. 1911, Oxford Medical Publications, London, p. 125.
8. Wendt, E. C.: A treatise on Asiatic cholera. 1885, William Wood and Co., New York, p. 257.
9. Chatterjee, S. C.: Symmetrical peripheral gangrene in lobar pneumonia. Calcutta Med. J. **37**: 221, 1940.
10. Davoli, E.: Gangrenous purpura associated with meningococcemia. Clin. Proc. Child. Hosp. **14**: 232, 1958.
11. Philips, V. K.: Acute meningococcemia with symmetrical peripheral gangrene: report of a case. Ann. Intern. Med. **48**: 864, 1958.
12. Weil, M. H., Spink, W. W.: The shock syndrome associated with bacteremia due to gram-negative bacilli. Arch. Intern. Med. **101**: 184, 1958.
13. Lutembacher, R.: Endocarditë subaiguë et endartérite pulmonaire chez les cardiaques. Arch. d. mal. du cœur **10**: 353, 1917.
14. Cockayne, E. A., Wilton, T. N. P.: Acute bacterial endocarditis; two unusual cases. Lancet **2**: 728, 1941.
15. Storstein, O.: Incipient symmetrical peripheral gangrene complicating pneumonia. Brit. Heart J. **13**: 411, 1951.
16. Uhr, J. S.: Gangrene of the toes following pneumococcemia; treatment with sulfanilamide. Amer. J. Dis. Child. **56**: 1317, 1938.

EDITORIALS

DOOMSDAY, A. D. 2026?

FROM my study I look across the valley to my son's brand-new junior high school gleaming on the hill. Built to relieve the crowding in the recently constructed high school, this new building is surrounded already by a multitude of even newer houses mushrooming up in fields and woods that were wild and empty in my own boyhood. Where there was solitude there now are people; where there are people there soon will be babies; where there are babies there are more people. The view from my window encompasses a tiny but definite segment of one of the great crises that face man today.

The population of the world, in round numbers, was 250 million at the beginning of the Christian Era.[1] By 1650 the number of people living on the planet had doubled to 500 million. In the last 300 years the number increased five-fold to the present level of 2500 million or 2.5 billion. Each day 140,000 more humans are born than die; in 40 years, by the end of the century, there will be five billion people or twice again as many as there are now. These appalling data clearly pose a series of problems, not the least of which is the "inexorable problem of space"—at some point in time there will be standing room only.[2] In a recent article in *Science*[3] the authors extrapolate the known data on the human populations of the last two millenia; the date derived for the point of approach to an infinite number of people is only 66 years away, A. D. 2026 ± 2,000 days. The authors (perhaps with tongue in cheek) pick Friday the 13th of November of that year as the "doomsday" on which your great-grandchildren and mine will no longer have room to breathe, let alone to stand. More conservative demographic estimates put off this dire point for another 700 years.[2] But even if our great-grandchildren have room to breathe, they are going to be overcrowded.

This population explosion has been the subject of much recent discussion. And so it should be, for it has grave implications for the whole human race, implications that go far beyond the urbanization of our countryside, the crowding of our schools, the absence of a place to park beside the supermarket. At the Darwin Centennial Celebration, held a little more than a year ago at the University of Chicago, the population explosion was held to be one of the three major problems in the world today (the other two are the prevention of thermonuclear warfare and the raising of the standard

[1] Hauser, P. M.: Demographic dimensions of world politics. Science **131**: 1641–1647, June 3, 1960.

[2] Sears, P. B.: The inexorable problem of space. Science **127**: 9–16, Jan. 3, 1958.

[3] von Foerster, H., Mora, P. M., Amiot, L. W.: Doomsday: Friday, 13 November, A.D. 2026. Science **132**: 1291–1295, Nov. 4, 1960.

of living in the underprivileged nations).[4] Just as Charles Darwin and his leading champion, Thomas Huxley, strove to place the evolution of living species in a new and true perspective, so their grandsons, Sir Charles Darwin and Sir Julian Huxley, along with many others, strive to place in perspective the biologic and social problem of the explosive expansion in numbers of the dominant species, man.

Students of the problem have been divided into two groups, the optimists and the pessimists.[3, 5] The former believe that as a result of the unlimited ingenuity of man any increase in numbers can be met by an adequate increase in production of food and natural resources. The latter, from Malthus to Sir Charles Darwin,[6] see only more and more unfed mouths unless war and pestilence supervene. They point out that, short of actual starvation (or being squeezed to death), a lower standard of living will lead inevitably to political instability, loss of freedom, and debasement of dignity of the individual man. In an already precarious world this is pessimism indeed.

But perhaps there is a middle ground for cautious hope. The S curve of animal populations which ends in a final stage of low fluctuation and stability of numbers is well-known.[5] Likewise the human population over the long past has stabilized after each of the rapid expansions that took place with the cultural revolutions of tool-making, agriculture, and industrialization.[7] In these earlier stabilizations the restraints were more than the external environmental factors of limitation of food and other natural resources; internal restraints of culture as well as of warfare must have played a role. Warfare restrains numbers by increasing the death rate; the same may be said for the hardly less rational periodic rush of the lemmings to suicidal immersion in the Arctic seas. Education and civilization are usually associated with restraint on the rate of reproduction. The reproductive rate may be responsive to subtle and poorly understood factors that operate below the level of consciousness. For instance, there is experimental evidence to suggest that mental stress from overcrowding may lead, via the pituitary-adrenal-gonadal axis, to diminished sexuality and relaxed parental care. But the evolutionary advantage of man is his cerebral cortex. It is because of this superior organ that he has emerged into a new and unique phase of evolution, a phase that according to Sir Julian Huxley is governed by psychosocial selection rather than by natural selection.[8] For this reason man's greatest hope for regulation of his numbers lies in the rational control of the rate of birth.

[4] Evolution after Darwin, Vol. III, *Issues in Evolution*, edited by Tax, S., and Callender, C., pp. 49, 64. The University of Chicago Press, Chicago, 1960.

[5] McKelvey, V. E.: Resources, population growth, and level of living. Science **129**: 875–881, April 3, 1959.

[6] Darwin, C. G.: Can man control his numbers? Perspect. Biol. Med. **3**: 252–263, Winter 1960.

[7] Deevey, E. S., Jr.: The human population. Sci. Amer. **203**: 195–204, Sept. 1960.

[8] Huxley, J.: The emergence of Darwinism. Perspect. Biol. Med. **3**: 321–342, Spring 1960.

The physician in particular, and mankind in general, has been concerned primarily with the control of death. A refinement of such concern is set forth in the following editorial which considers the quality of certain genetic replications that may critically affect the making of a man. But enhancement of genotypic quality to produce phenotypic longevity (delayed death of the individual) may be set quite at naught by the mere quantity of replications, by an avalanche of uncoiling helices of DNA molecules, by a smothering mass of human protoplasm. The absolute necessity for control of the birth rate, whatever the difficulties in its accomplishment, should be apparent to every physician as a human biologist and to every thoughtful member of the human race.

Failure to bring under control the reproductive rate of the race will surely lead to a moral decline and to an unbridled death rate. Let all men beware of disregard of this problem lest the Four Horsemen of the Apocalypse ride again in this age of thermonuclear weapons. Then indeed will there be a more terrible doomsday, then indeed will the problem be solved—but hardly for the benefit of the late human race.

J. R. E.

HEREDITY AND DISEASE *

As man conquers disease caused directly by environmental factors (physical, chemical, and biologic), he turns his attention to diseases which are dependent largely or in part upon individual constitution, or genetic endowment. Of course, disease per se is not inherited, but the genes which comprise one's genetic endowment, or genotype, are inherited. Disease is a function of the somatic state, or phenotype, of an individual in a particular environment. The phenotype, in turn, is determined to a large extent by genotype. It is the purpose of the present review to discuss genotypic abnormalities which may be factors in disease, the methods available for the recognition of these genetic factors, and some physiologic and population aspects of the problem of heredity and disease.

The thousands of genes of man occupy sites (loci) on the 22 paired autosomal chromosomes and the sex chromosomes (X and Y). At a particular gene locus there may be any one of a set of gene variants, called *alleles*. Thus, at the ABO blood group locus there are O, A, or B alleles. The detection of an abnormal allele depends upon its production of a phenotypic effect. If this effect is produced even when the normal allele is present (i.e., in a heterozygous condition), the abnormal gene effect is said to be dominant; if it is produced only when the normal allele is absent (i.e., in a homozygous condition), the abnormal gene effect is said to be *recessive*.† These two types of abnormal genes display different patterns of inheritance

* From the Department of Pediatrics, City of Hope Medical Center, Duarte, California.

† Although it is the gene effect which is dominant or recessive, it is common practice to refer to the allelic genes producing these effects as dominant or recessive genes.

in families, i.e., the first shows dominant inheritance and the second, recessive inheritance.

1. *Diseases Manifesting Dominant Inheritance.* The inheritance of an autosomal dominant gene is characterized by its passage from generation to generation to one-half of the offspring of a mating of a normal and a heterozygous individual. (The special case of a dominant gene on a sex chromosome is too rare to warrant discussion here; see Neel and Schull.[1]) Well-known examples of dominant inheritance include achondroplasia, osteogenesis imperfecta, and Huntington's chorea.

The inheritance of a characteristic may not follow the anticipated pattern. For example, the common form of premature baldness observed in adult males is generally attributable to a single dominant gene. However, the appearance of baldness in one-half of the progeny is limited to the males. Nevertheless, it may be presumed that one-half of the female offspring carry the abnormal gene, inasmuch as their sons may be bald. Baldness may occur in a woman with an adrenocortical tumor and be relieved by surgical removal of the tumor. The presence of the abnormal allele in female heterozygotes does not produce an effect except under special conditions. A gene which produces an effect in some individuals but not in others is said to show *incomplete penetrance.* Many examples of dominant genes with incomplete penetrance have been reported. In some instances—for example, baldness—penetrance is largely a matter of sex limitation; in other instances there is no apparent explanation. In general it may be stated that penetrance may depend upon either genetic or environmental factors.[2]

Another type of deviation from expected inheritance is illustrated by osteogenesis imperfecta. In its classical form this disease is characterized by brittle bones, blue sclerae, and deafness. However, some individuals in a pedigree demonstrate only one or two of this triad of symptoms, and the symptoms may vary considerably in intensity from person to person. This *variable expressivity,* like incomplete penetrance, may also be due to either genetic or environmental factors.

Osteogenesis imperfecta is also of considerable interest because more than one phenotypic effect is produced by a single gene, i.e., the gene is *pleiotropic.* There are reports in the literature which attribute such multiple effects to abnormal alleles at two or more gene loci which are physically close to each other on the same chromosome (such loci are said to exhibit *linkage*). If this were the case, however, one would expect to find the most common pedigrees to be those in which only one of the closely linked genes is abnormal. It is emphasized that penetrance, expressivity, and pleiotropism are related phenomena. For example, it is expected that a loss of one of the phenotypic effects of a pleiotropic gene will produce a variation in ex-

[1] Neel, J. V., Schull, W. J.: Human heredity, Chapter 6, 1954. University of Chicago Press.

[2] Stern, C.: Principles of human genetics, 2nd Ed., Chapter 16, 1960. W. H. Freeman and Company, San Francisco.

pressivity, while a complete failure of expression will produce a lack of penetrance. The problems of penetrance, expressivity, and pleiotropism are well discussed by McKusick [3] in connection with osteogenesis imperfecta and other disorders of connective tissues.

Erythroblastosis fetalis depends for its expression upon both genetic and nongenetic factors. Affected individuals are heterozygous for negative and for positive Rh factors, having derived the former from the mother and the latter from the father. Furthermore, they must receive, via the placental circulation, a maternally produced antibody against their erythrocytes. Consequently, only a small number of heterozygous individuals actually develop the condition. The Rh system also illustrates well the problem of allelism, there being a number of positive Rh gene substitutions possible. (It is still a controversial question whether the Rh character is determined by a set of closely linked gene loci or by one gene locus.)[4]

Just as it is true that nongenetic factors may be necessary for the expression of a gene effect, so it is also true that nongenetic factors may produce effects which mimic those produced by abnormal genes. For example, cleft palate is a condition sometimes attributable to an incompletely penetrant, dominant gene. There are, on the other hand, many sporadic cases of cleft palate, presumably nongenetic in origin. Such *phenocopies* are particularly common in the case of congenital anomalies, such as congenital heart disease. This situation is especially difficult to assess when genetic counseling is desired. If it cannot be established whether a particular case is genetically or nongenetically determined, reliance must be placed on the empirical data of past experience. The probability that a relative of an affected individual will be similarly affected is referred to as the *empiric risk*. Published tables which state the empiric risks for a number of conditions are useful to the genetic counselor.[5]

Achondroplasia is a dominantly inherited condition in which usually both parents of the affected individual are normal. That such individuals are not phenocopies is demonstrated by the fact that one-half of their offspring are affected. The most likely explanation for such a phenomenon is that a mutation from a normal to an abnormal allele of a gene has occurred in one of the germ cells producing such a person. The frequency of such mutant individuals has been used to estimate the mutation rate of the gene.[6]

Retinoblastoma is a frequently fatal condition often caused by a dominant gene.[7] A gene which produces a condition invariably fatal before the age

[3] McKusick, V. A.: Heritable disorders of connective tissues, 2nd Ed., Chapters 1, 5, 1960. C. V. Mosby Co., St. Louis.

[4] Wiener, A. S., Owen, R. D., Stormont, C., Wexler, I. B.: Medicolegal applications of blood grouping tests. J. A. M. A. **164**: 2036, 1957.

[5] Böök, J. A.: Heredity counseling: medical genetics and counseling practices. Eugenics Quart. **2**: 174, 1955.

[6] Slatis, H. M.: Comments on the rate of mutation to chondrodystrophy in man. Amer. J. Hum. Genet. **7**: 76, 1955.

[7] Macklin, M. T.: A study of retinoblastoma in Ohio. Amer. J. Hum. Genet. **12**: 1, 1960.

of reproduction is called a *lethal* gene. Lethal genes are self-eliminating from a population and are maintained only by mutation. Ordinarily there is no obvious way to determine whether such a condition is of genetic origin. However, in the case of retinoblastoma some affected persons are saved by virtue of surgery and grow to adulthood and reproductive capacity. It may then become apparent from the occurrence of the condition in their progeny that the condition is hereditary. If such a dominant gene is completely lethal, its frequency in the population is equal to the mutation rate (designated μ and expressed as a number per genetic locus), and the frequency of the disease (H) is twice that frequency, since each person has that mutation probability for each of the two genes of an autosomal pair ($H = 2\mu$). From this it follows that any factor which increases mutation rate correspondingly increases the incidence of the disease. If the patient survives through treatment the frequency of the abnormal allele may increase. If the survival value of normal individuals is denoted as 1.0, and of individuals with a fatal condition as 0.0, then individuals with an irregularly fatal condition have a survival value of 1–s. It is apparent from the illustration of retinoblastoma that (s), the coefficient of selection, is subject to change.

Huntington's chorea is an example of a dominantly inherited condition whose onset is toward the end of the reproductive period in man. This gene, present at birth, does not produce its phenotypic effect until a remote time. Huntington's chorea is also interesting because it is a fatal condition even though the gene producing it is only partially lethal ($s = 0.2$),[8] i.e., generally speaking, the gene is not immediately self-eliminating from the population because the disease it causes is not lethal until after the age of reproduction. It is apparent from this and from prior discussion that the frequency of a dominant gene in a large population is determined rather directly by the mutation rate of the gene and by the survival value of affected individuals in a particular environment. (The general problem of the frequency of a gene in a large population as a function of the mutation rate and phenotypic value is thoroughly discussed by Li.[9])

The important discovery of the role of chromosomal abnormalities in human disease (recently reviewed in this journal[10]) should serve to remind us that dominant inheritance may involve an abnormality in a portion of a chromosome which is larger than a single gene locus. Thus Tjio, Puck, and Robinson[11] have reported chromosomal abnormalities in Marfan's syndrome, a condition which characteristically displays dominant inheritance. McKusick[12] has questioned the diagnosis in this report, however. In

[8] Reed, T. E., Neel, J. V.: Huntington's chorea in Michigan: 2. Selection and mutation. Amer. J. Hum. Genet. **11**: 107, 1959.

[9] Li, C. C.: Population genetics, Chapters 18–20, 1955. University of Chicago Press.

[10] Ferguson-Smith, M. A., Johnston, A. W.: Chromosome abnormalities in certain diseases of man. Ann. Intern. Med. **53**: 359, 1960.

[11] Tjio, J. H., Puck, T. T., Robinson, A.: The human chromosomal satellites in normal persons and in two patients with Marfan's syndrome. Proc. Nat. Acad. Sci. **46**: 532, 1960.

[12] McKusick, V. A.: Chromosomes in Marfan's syndrome. Lancet **1**: 1194, 1960.

another condition, the Sturge-Weber syndrome, which is generally attributed to a dominant gene, trisomy for chromosome 22 has been reported recently.[13] Even the usual form of mongolism, which involves trisomy for chromosome 21, may be transmitted dominantly,[14] although the fertility of mongols is so low that it is of no practical significance. Clearly, one of the most important tasks of clinical cytogeneticists is the examination of recognized dominantly inherited conditions for chromosomal abnormalities.

2. *Diseases Manifesting Recessive Inheritance.* Recessive genes are more commonly the cause of disease than are dominant genes. The phenotypic disease associated with an autosomal recessive gene is manifest only in homozygous individuals; that associated with a sex-linked gene may be manifest in a male with only one abnormal gene since no normal homolog is present. (Only nonhomologous X-linkage is discussed here. The special cases of homologous X-linkage and of Y-linkage are discussed by Neel and Schull,[1] in chapter 7.) Albinism, galactosemia, and most of the serious inborn errors of metabolism demonstrate autosomal recessive inheritance. Hemophilia, pseudohypertrophic muscular dystrophy, and nephrogenic diabetes insipidus demonstrate sex-linked recessive inheritance.

The analysis of family data is more complicated in the case of a recessive gene than a dominant gene. This is occasioned by the fact that, although the expectation of a child's being affected when both parents are heterozygous is one chance in four, the families are not ordinarily identified by the heterozygous parents, but rather by the occurrence of a case among the children. Matings of two heterozygous parents fortunate enough not to have a case are therefore not identified. The fraction of affected children in a sibship under these conditions decreases with increasing size of sibship, since fewer families with a large number of children remain unidentified for lack of a case, for example:

FRACTION OF CHILDREN AFFECTED

Size of Sibship	All Matings	Matings Producing an Affected Child
1	0.25	1.00
2	0.25	0.57
3	0.25	0.43
4	0.25	0.37
5	0.25	0.33
10	0.25	0.26

In the case of twin pairs containing at least one affected individual the fraction of affected individuals is 1.00 for identical twins and 0.57 for fraternal twins. (Complete ascertainment of cases is assumed here [truncate selec-

[13] Hayward, M. D., Bower, B. D.: Chromosomal trisomy associated with the Sturge-Weber syndrome. Lancet **2**: 844, 1960.

[14] Lehman, O., Forssman, H.: Chromosome complement in a mongoloid mother, her child, and the child's father. Lancet **1**: 498, 1960.

tion].) For a discussion of tests of the recessive hypothesis with this and other types of ascertainment see Steinberg [15] and Morton.[16]

Sickle cell anemia is a well-known example of a disease attributable to a recessive gene whose presence can be detected in the heterozygote. Recent evidence indicates that heterozygotes may also be identified as carriers of the genes responsible for galactosemia and for phenylketonuria, and that success may be anticipated for other conditions as well.[17] Theoretically at least this would make possible the complete ascertainment of the results of matings of two heterozygous individuals, a point of considerable importance in genetic counseling.

Despite the high mortality rate of sickle cell anemia its frequency is remarkably high in some Negro populations. It is believed now that this has resulted from selection *for* the heterozygous carrier of the sickle cell allele. Apparently such heterozygous persons are relatively resistant to falciparum malaria, whereas normal homozygous persons are much less so.[18, 19] Therefore in an area where this disease is endemic, normal alleles of this gene are lost because of deaths of normal individuals from malaria; there is a resultant increase in the number of heterozygous persons; and, finally, an increase in the number of abnormal homozygous persons with sickle cell anemia, whose deaths lead to the loss of abnormal alleles. Ultimately a genetic equilibrium is reached (*balanced* polymorphism). The equilibrium frequency of the gene ($\hat{q}$) in a given population is related to the coefficient of selection (s) for the normal homozygote as follows:

$$\hat{q} = \frac{s}{1+s}, \quad \text{and} \quad s = \frac{\hat{q}}{1-\hat{q}}.$$

For example, if the survival values and coefficients of selection are as follows:

$1 - s_1 = 1.0$ $\quad s_1 = 0.0$, for the heterozygote
$1 - s_2 = 0.0$ $\quad s_2 = 1.0$, for the abnormal homozygote (i.e., lethal)
$1 - s_3 = 0.95$ $\quad s_3 = 0.05$, for the normal homozygote

then $\hat{q}$, the frequency of the gene at equilibrium, is approximately 0.05, and the frequency of heterozygotes is approximately 10%, of normal homozygotes about 90%, and of abnormal homozygotes about 0.25%. Obviously, the elimination of falciparum malaria would have a great effect upon the frequency of sickle cell anemia.

[15] Steinberg, A. G.: Methodology in human genetics. Amer. J. Hum. Genet. **11**: 315, 1959.

[16] Morton, N. E.: Genetic tests under incomplete ascertainment. Amer. J. Hum. Genet. **11**: 1, 1959.

[17] Hsia, D. Y.: Recent advances in biochemical detection of heterozygous carriers in hereditary disease. Metabolism **9**: 301, 1960.

[18] Allison, A. C.: Malaria in carriers of the sickle-cell trait and in newborn children. Exp. Parasit. **6**: 418, 1957.

[19] Motulsky, A.: Metabolic polymorphisms and the role of infectious diseases in human evolution. Hum. Biol. **32**: 28, 1960.

Most recessively inherited diseases, such as albinism, phenylketonuria, and galactosemia, are quite rare. Selection is against the abnormal homozygote, so there is continuous gene loss. However, mutations from the normal to the abnormal allele continually counteract this gene loss. When the two processes are exactly opposed, an equilibrium is reached and the frequency of the disease in question may thus remain the same in successive generations. If there is no selection for or against the heterozygous individual, the mutation rate (frequency of mutation of a normal allele to an abnormal allele of a particular gene per generation), is equal to the disease incidence for a uniformly fatal disease that is recessively inherited. Thus, as in the case of dominantly inherited disease, an increase in mutation rate from any cause results in an increase in disease frequency.[20, 21]

An individual homozygous for a recessive gene has received the abnormal gene from each parent. It follows then that rare recessive conditions should have an increased incidence among consanguineous matings, since the parents have an increased chance of having the same abnormal genes. As a matter of fact, the frequency of a recessive gene (q) in a given population is related approximately to the incidence of first cousin marriages in that population (c) and to the observed incidence of first cousin marriages among the parents of affected individuals (k), as follows:

$$k = \frac{c}{16}\left(\frac{1}{q} + 15\right).$$

As (q) becomes larger (k) becomes insignificantly different from (c). It is worthy of note that the sudden elimination of matings between cousins would immediately reduce the incidence of a rare disease. However, since the abnormal genes are eliminated by death of the homozygote, the rate of elimination of the particular gene would decrease and the frequency of the gene would increase until the original equilibrium disease frequency be reached again. (For a detailed account of inbreeding see Li,[9] chapter 16.)

Albinism has a high frequency among the San Blas Indians, who live on a group of small islands off the coast of Panama. This is a small isolated population with an unusually high frequency of this abnormal gene. How did this frequency come to be? Although heterozygotic selection may be a factor, this situation probably illustrates another way in which a gene frequency may attain an elevated value. This is the mechanism whereby chance variations in gene frequency occur from one generation to another in small populations. For example, consider a population of 10,000 of whom 1% are heterozygous for a particular allele. The frequency will not change greatly in a random manner from generation to generation. If the population is now divided into 100 groups of 100 each, some groups will have 0,

[20] Crow, J. F.: The estimation of spontaneous and radiation-induced mutation rates in man. Eugen. Quart. 3: 201, 1956.

[21] Crow, J. F.: Possible consequences of an increased mutation rate. Eugen. Quart. 4: 67, 1957.

some 1, some 2, etc., heterozygous persons. The heterozygote frequency will correspondingly be 0%, 1%, 2%, etc., and a large deviation from the original 1% would be possible. Thus, the frequency of a particular gene in an isolated sub-population may be very different from its frequency in the large parent population. One of the effects of the elimination of population isolates in the twentieth century is the reduction of the incidence of particular diseases which have high frequencies in these isolates. (The genetics of small population groups is a special subject discussed by Li,[9] chapter 22, and by Wright.[22]

No matter what measures man may take to control his own evolution, it is very probable that he will still have to contend with heritable disorders. In some instances the prevention or treatment of disease in individuals with abnormal genotypes may be a relatively simple matter. For example, the hemolytic anemia produced by fava beans and certain chemicals related to primaquine depends upon both genetic and environmental factors.[23] Elimination of the latter factor prevents genetic penetrance and disease. It will undoubtedly be shown in the future that many conditions belong in this category. We already suspect that both genetic and environmental factors are present in such conditions as allergic disorders and the rheumatic diatheses.

There remains a number of serious conditions in which heredity is the major factor, i.e., penetrance is virtually complete. Particularly in those diseases in which recessive inheritance is observed the responsible hereditary factor is probably a single abnormal gene (in the homozygous state). If such homozygotes cannot be avoided by selection, then therapeutic measures must be sought. Such measures must answer one of the following questions: (1) How can an individual's genotype be transformed? (2) How can an individual's phenotype be made normal if the genotype remains abnormal? Although there is hope for an answer to the first of these questions from the work done on transformation [24] and transduction [25] in bacteria, and perhaps from some evidence on transformation in ducks,[26] there is no promise of therapeutically useful transformation measures at the present time. On the other hand there is a good theoretic approach to the second question and even therapeutic measures for a few diseases.

Galactosemia is a well-known example of a recessively inherited disease, in which the institution of a special diet at an early age prevents disease.

[22] Wright, S.: Physiological genetics, ecology of populations, and natural selection. Perspect. Biol. Med. **3**: 107, 1959.

[23] Beutler, E.: The hemolytic effect of primaquine and related compounds: a review. Blood **14**: 103, 1959.

[24] Hotchkiss, R. D.: Bacterial transformation. J. Cell. Comp. Physiol. **45**: (Suppl. 2) 1, 1955.

[25] Hartman, P. E.: Transduction: a comparative review. *in* The chemical basis of heredity (edited by W. D. McElroy and B. Glass), p. 408, 1957, Johns Hopkins Press, Baltimore.

[26] Benoit, J., Leroy, P., Vendrely, R., Vendrely, C.: Experiments on Peking ducks treated with DNA from Khaki Campbell ducks. Trans. N. Y. Acad. Sci., Series II **22**: 494, 1960.

A galactose-free diet averts the accumulation of galactose-1-phosphate, which is considered to be a disease-producing substance. Galactose-1-phosphate accumulates because it is formed from galactose as usual but does not react with uridine diphosphate glucose to give glucose-1-phosphate and uridine diphosphate galactose. This latter reaction fails for lack of a transferring enzyme.[27] Therapy avoids the consequences of the metabolic block.

In several forms of recessively inherited goiter there is a block in the synthesis of thyroxine.[28] In this case the problem arises not only from the accumulation of a substrate but from the failure of formation of the product of the reaction. Circumvention of this metabolic block is accomplished by supplying the product, viz., thyroxine.

In each of the above examples circumvention of the defect can be accomplished relatively directly. However, it is likely that many inborn errors of metabolism involve sites far removed from dietary substances, so that averting the synthesis of an accumulating substrate becomes much more complicated. One method for interrupting a synthetic pathway is the use of antimetabolites, such as MER-29, an inhibitor of cholesterol synthesis, which may prove to be useful in treating idiopathic hypercholesteremia.[29] Because this method offers highly specific interference it may find general use in the management of metabolic errors.

Another possible therapeutic method would be direct correction of the enzyme defect. Since enzymes are proteins, the more general solution is correction of protein defects. This might be done by altering the abnormal protein (made under the influence of an abnormal gene) in such a way that it can perform a normal function. Before such reversion can be attempted there is need for knowledge of the nature of the defect in the abnormal protein. In one instance, viz., the hemoglobinopathies, such knowledge is available. Hemoglobin consists of four cross-linked peptide chains, two of one type (α), and two of another type (β). In hemoglobin S a glutamic acid residue in each β chain is replaced by valine.[30] In hemoglobin C the same glutamic acid residue of the β chains is replaced by lysine.[31] In hemoglobin E a different glutamic acid residue of the β chains is replaced by lysine.[32] There are other hemoglobinopathies which involve the α chain. Since the abnormal genes which control the β chain alterations behave as

[27] Isselbacher, K. J.: Galactosemia. *in* The metabolic basis of inherited disease (edited by J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson), chapter 7, page 208, 1960. McGraw-Hill Book Co., Inc., New York.

[28] Stanbury, J. B.: Ibid., chapter 9, page 273.

[29] Avigan, J., Steinberg, D., Thompson, M. J., Mosettig, E.: Mechanism of action of MER-29, an inhibitor of cholesterol biosynthesis. Biochem. Biophys. Res. Comm. **2**: 63, 1960.

[30] Ingram, V. M.: Abnormal human haemoglobins. III. The difference between normal and sickle cell haemoglobins. Biochem. Biophys. Acta **36**: 402, 1959.

[31] Hunt, J. A., Ingram, V. M.: Abnormal human haemoglobins. IV. The chemical difference between normal human haemoglobin and haemoglobin C. Biochem. Biophys. Acta **42**: 409, 1960.

[32] Hunt, J. A., Ingram, V. M.: Abnormal human haemoglobins: human haemoglobin E: the chemical effect of gene mutation. Nature **184**: 870, 1959.

alleles and as members of a locus distinct from those affecting the α chain, it has been hypothesized that genes control the synthesis of peptide chains, and that separate sites within the gene locus control separate aminoacid residues within the peptide chain. Apparently each site may have more than one allele. This hypothesis has been supported by the finding of individuals who are heterozygous at each locus and who have four distinct hemoglobins, as predicted.[33] However, despite the knowledge that a gene abnormality results in a peptide chain abnormality, we still do not have a means for manipulating the latter. That such an approach is promising is suggested by the report of Beutler [34] that sickle hemoglobin may be modified in vivo.

Finally, of course, the protein in question could be supplied artificially. Actually this is done when a patient with sickle cell anemia is transfused with normal blood. The protein could also be supplied indirectly by providing the mechanism for its synthesis, e.g., by tissue transplantation from a normal individual. The whole problem of tissue transplantation immunity and acquired tolerance is therefore of considerable interest to the human geneticist.

In summary, an attempt has been made to survey our present understanding of heredity and disease. Rational attempts to prevent hereditary disease require knowledge of the detection of abnormal genotypes, the segregation of genetic elements within families, their genesis, distribution and behavior in populations, and their interaction with environmental agents. Therapeutic attempts may be aided greatly by knowledge about the physiologic mechanism of gene action. Much has happened in the past decade to make us feel optimistic about man's control of his constitution as well as his control of his environment.

ALFRED G. KNUDSON, JR., M.D., PH.D.

[33] Atwater, J., Schwartz, I. R., Tocantins, L. M.: A variety of human hemoglobin with four distinct electrophoretic components Blood **15**: 901, 1960.

[34] Beutler, E.: The effect of in vivo modification of sickle hemoglobin on a patient with sickle-cell disease. Clin. Res. **8**: 101, 1960.

BOOK REVIEWS

1. *Modern Occupational Medicine.* 2nd Ed. Editors: A. J. Fleming, M.D., M.Sc. F.A.C.P., and C. A. D'Alonzo, M.D., F.A.C.P. Associate Editor: J. A. Zapp Ph.D. 587 pages; 15.3 × 22.9 cm. Lea & Febiger, Philadelphia, Pa. 1960. Price, $12.00.

2. *Occupational Diseases and Industrial Medicine.* By Rutherford T. Johnstone, M.D., and Seward E. Miller, M.D. 482 pages; 25.5 × 16.5 cm. W. B. Saunders Company, Philadelphia, Pa. 1960. Price, $12.00.

These two books actually complement each other in their approaches to the subject of occupational medicine. Drs. Fleming, D'Alonzo, and Zapp devote a great deal of space to general discussions of the organization and problems of a department of occupational medicine. Their book is divided into eight sections. The first section (five chapters) deals with organization of such a department. The second section (four chapters) covers industrial preventive medicine. Section three (five chapters) discusses physical environment, work, stress, and occupational health. The fourth section (nine chapters) deals with the services allied to occupational medicine. Section five (four chapters) covers psychiatry; section six, (six chapters) toxicology; and the last two sections, each of only one chapter, cover acute poisoning and biostatistics, respectively. For the physician who is asked to set up an integrated medical department for a large industry, the book contains a wealth of useful information and helpful, practical suggestions. It clearly depicts the very wide range of interest and knowledge with which the modern industrial medical department in a large diversified industry must concern itself. As its authorship implies (some 22 individual authors, all with the Du Pont Company, contributed to the various sections), industrial medicine is a highly complicated specialty, requiring the assistance of men skilled in a great variety of disciplines, if an adequate solution to most of industry's medical or medically related problems is to be realized.

The book by Drs. Johnstone and Miller is divided into two sections. The first (seven chapters) deals with the practice of industrial medicine, but not in the detail discussed by Fleming et al. The second section (13 chapters) covers the occupational diseases in a more satisfying way for the part-time physician or for the industrial physician who has little if any additional help. In Chapter 4, a useful tabular summary of State Workmen's Compensation Laws is provided. An appendix of Threshold Limit Values for 1959 and 1960 is included. In addition, the book is dotted with interesting and illuminating case reports which illustrate the material presented.

The Johnstone and Miller book is a must for any physician who spends a portion of his time in giving occupational medical service. As his interest develops and his responsibility for service grows, the Fleming, D'Alonzo, and Zapp book would be a natural addition to his reference shelf; it should be in the library of any full-time industrial physician.

R. E. Eckardt, M.D.

A Clinical Prospect of the Cancer Problem. Neoplastic Disease at Various Sites. Edited by D. W. Smithers, M.D., F.R.C.P., F.F.R. 232 pages. Published by E. & S. Livingstone, Ltd., Edinburgh and London, available in the U. S. through The Williams and Wilkins Company, Baltimore, Maryland. 1960. Price, $8.50.

This book is intended as the first in a series of monographs on neoplastic disease by various authors to be edited by Dr. Smithers, Professor of Radiotherapy at the University of London. Dr. Smithers is both a contributor to and editor of the present volume, which is intended as a broad introductory view of the cancer problem. Dr. Smithers states in the preface that this is a personal view and intended to be specu-

lative, philosophic, and productive of discussion. As such, it is more difficult to criticize than would otherwise be the case.

The book is a handy size, and the printing and photography are of high quality. It is extremely "readable." As a pathologist, this reviewer deplores the repeated use of mixed tumor as an example of a metastasizing neoplasm and such statements as, "The thyroid provides the best example of this blood stream spread of apparently normal tissue." The relationship of viruses to neoplasia is given short shrift in the light of the intense activity current in this area. Dr. Smithers views cytology with a dubious eye, oddly enough being most enthusiastic about its value in urinary tract diagnosis. He is unduly pessimistic and critical of chemotherapy and especially of the chemotherapeutic screening program.

None the less, there is much of interest in this book. The subject of spontaneous regression of tumors is well covered, and the chapter on quackery and education is extremely thought provoking. On the whole, while uneven, this book is well worth the attention of those concerned with the cancer problem.

HORATIO T. ENTERLINE, M.D.

J.-M. Charcot, 1825–1893: His Life—His Work. By GEORGES GUILLAIN, M.D. Membre de L'Institute, Membre de L'Académie de Medicine. Edited and translated by PEARCE BAILEY, PH.D., M.D., Director, National Institute of Neurological Diseases and Blindness, Bethesda, Md. 202 pages; 21.5 × 14.5 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1960. Price, $7.00.

This interesting biography of the founder of modern clinical neurology deals not only with the life of Jean-Martin Charcot but with his contributions to medicine and with the famous institution, the Salpêtrière, in which he worked devotedly for 45 years.

Charcot followed the investigative methods which had been developed to a high point in French medicine during the first half of the 19th century—the comparison of observations of clinical phenomena with the pathologic findings post-mortem. In a discussion of his general philosophy of medicine he said: "Finally, I believe that, aside from questions of diagnostic ingenuity and other intuitive qualities which cannot be acquired by all, a physician is only as good a clinician as he is a pathologist." He lived by this creed, for he held for 10 years the rank of Professor of Pathological Anatomy in the Faculty of Medicine. At the end of this period, because of the importance of his contributions to clinical neurology and neuropathology, there was created for him the first professorial chair in the world for the diseases of the nervous system.

The author of the biography, Professor Georges Guillain, devotes half of the volume to admirably clear and brief discussions of the numerous neurologic diseases that were first differentiated clinically and anatomically by Charcot, among them multiple sclerosis, amyotrophic lateral sclerosis, and tabetic arthropathies. Together with others, Charcot made fundamental contributions to our knowledge of progressive muscular atrophy, aphasia, and the general subject of cerebral and spinal localization. Considering the primitive descriptions of neurologic disease prior to the era of Charcot it may be said that few men have played so large a role in laying the foundations of a new specialty.

The author has drawn an interesting picture of the professional and the personal life of one of the great clinicians and teachers of the latter half of the 19th century. The story of the Sâlpetrière and how Charcot transformed this ancient and vast asylum into an internationally prominent center for neurologic research and teaching is one which should be of special interest to those physicians in this country who are concerned with the problems of hospitals for chronic diseases.

The editor and translator, Dr. Pearce Bailey, has added greatly to the value of the volume with explanatory notes and a brief appendix on the organization of

French academic medicine. The publishers have provided a most attractive format and an interesting group of illustrations.

M. C. PINCOFFS, M.D.

Industrial Pulmonary Diseases: A Symposium Held at the Postgraduate Medical School of London, 18th–20th September, 1957, and 25th–27th March, 1958. Edited by E. J. KING, M.A., D.Sc., F.R.I.C.; and C. M. FLETCHER, C.B.E., M.D. (Cantab.), F.R.C.P. 269 pages; 22.5 × 14.5 cm. Little, Brown and Company, Boston. 1960. Price, $8.50.

Respiratory dysfunction associated with exposure to numerous irritating inhalants ranks high among the less desirable benefits of an industrialized society. Workers may be exposed directly in certain phases of industrial processes. Population groups are exposed indirectly because of the atmospheric pollution so common to industrial communities. In England, the Industrial Revolution during the early 19th century produced conditions which forced health officials, workers, employers, and government officers to recognize the relationship between polluted air and respiratory disease. British investigators ever since have retained interest in and gained knowledge of the effects of industrial atmospheres on the lung. In recent years, because of widespread incidence of chronic bronchitis and emphysema among older citizens, factors other than mere exposure to dust or fumes have been analyzed, such as cigarette smoking, automobile exhausts and smog, socio-economic levels, etc. Questions have been raised concerning the epidemiology of respiratory diseases in general. The need for careful observation of persons exposed to dusts and the necessity for deriving objective criteria to define disability have become apparent.

Industrial Pulmonary Diseases contains papers delivered at a symposium held at the Postgraduate Medical School, London, during 1958. In their presentations the authors consider the predominant features of the major pneumoconioses: silicosis, siderosis, byssinosis, and that due to tin oxide. Pathologic anatomy, pathophysiology, epidemiology, and diagnostic problems are discussed. Due attention is given to bronchitis in industry and to occupational lung cancer. Methods for minimizing exposure to and decreasing the hazards of industrial dust are described.

Features which are described in detail deserve mention. The effects of particle size in fall-out and the site of deposition of dust in the bronchoalveolar complex are considered. Damage to the respiratory bronchiole and adjacent structures by silica and other dusts is emphasized. The pathologists stress the influence of tuberculosis in production of massive fibrosis. Special radiologic problems inherent in mass surveys at industrial sites (Radiography in the Field) are carefully delineated. To assist the nonspecialist in analyzing abnormalities of pulmonary function tests, there is a clear, brief presentation of normal respiratory function and its measurement. A chapter describes in detail derangements of pulmonary function due to exposure to polluted atmospheres. The usefulness of function tests as adjuncts to epidemiologic studies relating exposure to dust, chest radiographic abnormalities, and functional disability is demonstrated. Practical considerations in selection of tests are covered at length.

In a brief period of time—the symposium lasted less than three days—and in a publication as short as this one, goals must of necessity be limited. Within these boundaries, a great deal has been accomplished by the participants in the educational endeavor represented by *Industrial Pulmonary Diseases*. Much more time, space, and detailed description could have been allotted to any of the subjects considered in the symposium. However, the terse style and interesting presentations outweigh the brevity and will rather attract than fend off the newcomer to this field. For those concerned, references are included which permit further study.

This small volume is full of information which will be of value to anyone interested in the lung, industry, or both. Matters pertaining to employee disability

and compensation, and to prevention of air pollution are assuming more prominence in industrialized societies with each year. In this symposium, public health officials, industrial physicians (including those associated with unions), and epidemiologists will find guides for devising programs to gather information relevant to these and related problems. Family doctors, medical educators, and medical students can gain insight into a segment of medicine which is increasing in scope. We are profoundly indebted to Drs. King and Fletcher and their colleagues for such a terse, clear, and useful book.

JEROME E. COHN, M.D.

Physiology of Prematurity: Transactions of the Fourth Conference, March 25, 26, and 27, 1959, at Princeton, New Jersey. Edited by JONATHAN T. LANMAN, M.D. 187 pages; 23.5 × 16 cm. The Josiah Macy, Jr. Foundation, New York. 1960. Price, $4.50.

The present volume extends this excellent series in the established, thought-provoking manner. The topics of the Fourth Conference included Heat Regulation, Hypothermia and Asphyxia of the Newborn, Chemical Structure, Functional Integration, and Renal Regulation as Factors in the (Homeostatic) Physiology of the Newborn.

The discussion of heat regulation lays heavy emphasis on developmental adaptation within the same species as well as from species to species. It is an excellent review and a stimulating interchange of new data and opinions.

The first section forms a natural foundation for the more controversial second section, which deals with hypothermia and asphyxia. This latter presentation and the discussion that follows it should be of great interest to both students and clinicians who are concerned with the physiologic and therapeutic implications of hypothermia and asphyxia. The pros and cons, as well as the current status of knowledge in this area, are well presented. Presentations of the salutary implications of normothermia to the human premature, and of some refreshing points of view on dehydration fever in early and in adult life, cap the discussion.

The third section deals with growth and chemical maturation as major homeostatic mechanisms in rapidly growing human and animal organisms. The discussion is fashionably oriented toward the "excellence" of renal function in early life, and even points out how much better the infantile kidney is in some respects than is the adult kidney, thus closing the circle of changing attitudes toward developmental renal physiology. These attitudes are even more interesting when expressed against the background of growth and chemical maturation as homeostatic mechanisms which are of far greater significance than has been emphasized before. The discussions of changing body composition are excellent and should prove useful to the clinician, the nutritionist, and the physiologist interested in the newborn and the rapidly growing young of both humans and the lower animals.

RAY HEPNER, M.D.

Diseases of the Newborn. By ALEXANDER J. SCHAFFER, M.D., with a section on Neonatal Cardiology by MILTON MARKOWITZ, M.D. 878 pages; 26 × 17.5 cm. W. B. Saunders Company, Philadelphia. 1960. Price, $20.00.

This new textbook is a comprehensive survey of both the normal and the abnormal conditions which can befall the neonate and which will require investigation and meditation by the attending physician. Drs. Schaffer and Markowitz have written in an extremely readable style—one entity follows another in a fluent, reasonable progression.

The chapters on Respiratory Disorders and Cardiovascular Disorders (the latter by Dr. Markowitz) are particularly fine examples of the completeness and

applicability of the book. The utilization of case material from the private practices of the authors and other physicians in their area provides a fascinating counterpart to the description of the entity just preceding it.

Numerous photographs, x-rays, and electrocardiograms provide visual stimulation and give the descriptions the qualities of bedside presentation. This clinical application of the material provides the most distinctive and valuable asset of this thorough, up-to-date, and worth-while text.

A. H. FINKELSTEIN, M.D.

Encyclopedia of Medical Syndromes. By ROBERT H. DUNHAM, M.D., F.A.C.P.; foreward by T. R. HARRISON, M.D. 628 pages; 24 × 16 cm. Paul B. Hoeber, Inc., New York. 1960. Price, $13.50.

Medical knowledge does not invariably lend itself to precise classification. A great variety of clinical observations, including those grouped into the medical syndromes, cannot be categorized by rational schemes. Most medical syndromes were described long before scientific knowledge permitted elucidation of underlying factors responsible for the features of the syndromes, but the original clinical descriptions have become an integral part of medical lore. Indeed, when basic etiologic factors are uncovered, eponymic or descriptive designations frequently are retained despite the obvious need for precise nomenclature.

Descriptions of the syndromes are scattered through medical, surgical, biologic, chemical, and related scientific publications. These notices often have appeared in journals with small circulations and limited audiences. This accounts in part for multiple descriptions of identical conditions, confusing terminology, and many-named entities.

The *Encyclopedia of Medical Syndromes* is the result of Dr. Durham's attack on this morass of scattered, disorganized information. He has collected and catalogued almost one thousand syndromes, which are arranged in alphabetical order. Synonyms for each of the titles are listed, and there are cross-references to other entities having equivalent or related symptoms and signs. Characteristic clinical features of the syndrome are recounted, and pertinent etiologic and pathologic information is recorded when available. Appropriate references to original articles are cited at the conclusion of each item, to assist the interested reader who might desire to expand upon the terse descriptive text. An extensive index is a valuable addendum to the volume. This portion is arranged by disease classification and organ system, so the reader can locate syndromes without prior knowledge of eponymic or other designations.

In compiling the syndromes in this manner, Dr. Durham has performed a considerable service for students of disease. Information is coördinated, and it is consolidated into a reference book to be consulted frequently. This volume may have the additional beneficial effect of sharply reducing unnecessary repetition in description and publication of constellations of symptoms and signs already defined as syndromes.

JEROME E. COHN, M.D.

Cardiac Auscultation, Including Audio-Visual Principles. 2nd Ed. By J. SCOTT BUTTERWORTH, M.D., MAURICE R. CHASSIN, M.D., ROBERT MCGRATH, M.D., and EDMUND H. REPPERT, M.D. 102 pages; 26 × 18 cm. Grune & Stratton, New York and London. 1960. Price, $6.25.

Since the first edition of this text appeared in 1955, significant advances have been made in audio-visual technics. In addition, other books have appeared which are devoted to various aspects of cardiac auscultation.

The present text incorporates several desirable features which were lacking in

the earlier edition. The stethograms are now recorded and illustrated with simultaneous electrocardiograms or pulse tracings. The hemodynamic data are more detailed, and the text itself is more physiologically oriented. Several criticisms which were made of the earlier edition are not applicable to the present edition. The chapter devoted to murmurs is extremely readable.

This text has not been intended as a comprehensive text of cardiology. It serves as an excellent introduction to cardiac auscultation, and as such it is warmly recommended to students. The illustrations are clear, and the diagrams aid the reader in following the text.

LEONARD SCHERLIS, M.D.

Diabetic Care in Pictures: Simplified Statements with Illustrations Prepared for the Use of the Patient. 3rd Ed. By HELEN ROSENTHAL, B.S., and JOSEPH ROSENTHAL, M.D. 237 pages; 24 × 15.5 cm. J. B. Lippincott Company, Philadelphia. 1960. Price, $4.50.

This pictorial handbook of practical day-to-day measures of diabetic care has been designed for the patient. There are brief discussions on the nature of diabetes mellitus, the various types of insulin and their uses, the early symptoms and signs of insulin reaction and diabetic acidosis and their proper treatment, and general measures of personal hygiene. This new edition also contains a chapter on the oral hypoglycemic agents and views them in proper perspective with regard to their place in therapy.

A large section is devoted to dietary treatment. The essentials of the normal and the diabetic diet are clearly outlined. The exchange systems for diet calculation of both the American Diabetes Association and the American Dietetic Association are outlined, and a large table of food values is included in the appendix. Numerous diagrams will help the patient to understand portion control. Special consideration is given to sodium restricted, bland, and low residue diets. Stress is put on the proper use of "dietetic foods."

Care of the syringe and needle (including sterilization procedure), and technics for filling the syringe and administering the insulin are described and pictured in a careful, step-by-step manner. Methods of testing the urine for sugar and acetone by several standard means are illustrated.

The authors, former heads of the Francis Stern Food Clinic and the Diabetic Clinic of the New England Medical Center, respectively, have had wide experience with the care and instruction of the diabetic patient. Their book emphasizes the supervisory role of the physician and the responsibility of the patient in the management of his disease under medical direction. It will prove useful to most patients, and especially to newly-discovered diabetics.

RICHARD DREWYER, M.D.

BOOK NOTICES

Sampling Microbiological Aerosols. Public Health Monograph No. 60, Public Health Service Publication No. 686. By HAROLD W. WOLF, M.S., PETER SKALIY, M.S., LAWRENCE B. HALL, M.S., and MARVIN M. HARRIS, Ph.D., Technical Development Laboratories; HERBERT M. DECKER, M.S., LEE M. BUCHANAN, B.S., and CHARLES M. DAHLGREN, B.S., U.S. Army Chemical Corps. 53 pages; 26 × 20 cm. (paper-bound). 1959. U. S. Department of Health, Education, and Welfare; for sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 45¢.

This comprehensive technical brochure provides a ready reference to anyone interested in biologic air analysis. The importance of monitoring and investigating air-borne contagion within medical environments needs no emphasis. Photographs,

descriptions, and technical data are presented on all types of impingers and samplers available for the collection and assay of biologic contaminants in air. In addition, the general considerations and limitations applicable to the isolation and enumeration of viable bacteria, fungi, viruses, and pollens are well discussed.

MERRILL J. SNYDER

Radiation: Use and Control in Industrial Application. Modern Monographs in Industrial Medicine, #5. (Editor-in-Chief: ANTHONY J. LANZA, M.D.; Consulting Editor: RICHARD H. ORR, M.D.) By CHARLES WESLEY SHILLING, M.D., D.Sc. 223 pages; 22.5 × 14.5 cm. Grune & Stratton, New York. 1960. Price, $6.75.

This well-written book provides a wealth of information in a little over two hundred pages. It is easily read and is very lucid, although in the interest of clarity a few minor theoretical errors are made in the exposition of some general principles. The book is well illustrated and a generous list of references is provided. It should certainly be of interest and value to everyone in the field of industrial medicine and might profitably be read by almost any physician.

M. J. W.

Biochemical Values in Clinical Medicine. The Results Following Pathological or Physiological Change. By ROBERT DUNCAN EASTMAN, M.D., D.C.P. 144 pages; 17.7 × 10.1 cm. John Wright & Sons, Ltd., Bristol; The Williams and Wilkins Company, Baltimore, Md., exclusive U. S. agents. 1960. Price, $3.75.

On a large number of body constituents and functional tests, Dr. Eastman has written brief articles giving normal values and the interpretations of abnormal findings. Some references follow each article.

EDWARD J. HUTH, M.D.

Nierenkrankheiten. By Prof. Dr. FRANCOIS REUBI. 758 pages; 24.8 × 18.1 cm. Medizinischer Verlag Hans Huber, Bern and Stuttgart. 1960. Price, DM 88.—

Dr. Reubi's comprehensive text covers the normal structure and function of the kidney, renal functional tests, the nature of kidney diseases—pathologic, clinical, and functional—and treatment. The book is well illustrated, with tissue sections, graphs, and tables; and the text is generously documented with citations from both the European and English-American literature. Careful printing, a clear and pleasant format, and a sturdy binding make the book physically attractive.

Ironically, despite the eminence of American and British nephrologists in the kidney world, they have not produced a text so comprehensive as this. Only H. E. de Wardener's shorter work, *The Kidney. An Outline of Normal and Abnormal Structure and Function,* stands as a competitor. American physicians, with their scanty knowledge of German, are likely to find Dr. Reubi's text most useful as a bibliographic source.

EDWARD J. HUTH, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. So far as is practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

A System of Medical Hypnosis. By AINSLIE MEARES, M.D. D.P.M. 467 pages; 16 × 24 cm. 1960. W. B. Saunders Company, Philadelphia. Price, $10.00.

Artefacts and Handling and Processing Faults of X-ray Films. By PROF. DR. E. A. ZIMMER. 67 pages; 17.2 × 24.1 cm. 1960. Grune & Stratton, Inc., New York and London. Price, $5.75.

Bedside Medicine. By I. SNAPPER, M.D. 561 pages; 15.5 × 23 cm. 1960. Grune & Stratton, Inc., New York. Price, $14.50.

Clinical Applications of Cardiopulmonary Physiology. By M. HENRY WILLIAMS, JR., M.D. 225 pages; 16 × 24.5 cm. 1960. Paul B. Hoeber, Inc., Medical Division of Harper Brothers, New York. Price, $7.50.

Clinical Vectorcardiography and Electrocardiography. By EDWARD MASSIE, M.D., and THOMAS J. WALSH, M.D. 572 pages; 20 × 26.5 cm. 1960. The Year Book Publishers, Inc., Chicago, Ill. Price, $27.50.

Congenital Malformations of the Heart. Rev. Ed., Vol. 1. By HELEN B. TAUSSIG, M.D. 197 pages; 17.8 × 25.5 cm. 1960. The Commonwealth Fund, Harvard University Press, Cambridge, Mass. Price, $4.75.

Letters to My Son. By WENDELL J. S. KRIEG, M.D., (Prof. of Anatomy, Northwestern University Medical School). 82 pages; 10.8 × 15.8 cm. 1960. Brain Books, Evanston, Ill. Price, $3.00.

Leukemia Cutis. By SAMUEL M. BLUEFARB, M.D., F.A.C.P. 482 pages; 14.5 × 22.4 cm. 1960. Charles C Thomas, Springfield, II. Price, $18.50.

Medicine as an Art and a Science. By A. E. CLARK-KENNEDY, M.D., F.R.C.P., and C. W. BARTLEY, M.D., D.M., M.R.C.P. 408 pages; 14.5 × 22.8 cm. 1960. J. B. Lippincott Co., Philadelphia. Price, $6.25.

Post-Basic Nursing Education Programmes for Foreign Students: Report of a Conference, Geneva, 5–14 October 1959. World Health Organization Technical Report Series No. 199. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. 47 pages; 24 × 16 cm. (paper-bound). Price, 60¢.

Rypin's Medical Licensure Examinations: Topical Summaries and Questions. 9th Ed. By WALTER L. BIERRING, M.D., M.A.C.P., M.R.C.P., with the collaboration of a Review Panel. 805 pages; 26 × 17.5 cm. 1960. J. B. Lippincott Company, Philadelphia. Price, $11.00.

Sea Within: The Story of Our Body Fluid. By WILLIAM D. SNIVELY, JR., M.D. 150 pages; 22.5 × 15 cm. 1960. J. B. Lippincott Company, Philadelphia. Price, $3.95.

A Syllabus of Laboratory Examinations in Clinical Diagnosis: Critical Evaluation of Laboratory Procedures in the Study of the Patient. Rev. Ed. Edited by LOT B. PAGE, M.D., and PERRY J. CULVER, M.D. 580 pages; 28 × 18.5 cm. 1960. Harvard University Press, Cambridge, Mass. Price, $12.50.

Treatment of Cardiovascular Emergencies. By ALDO A. LUISADA, M.D., Associate Professor of Medicine; and LESLIE M. ROSA, M.D., Assistant Professor of Medicine, Chicago Medical School. 122 pages; 17 ×10.5 cm. 1960. The Blakiston Division of McGraw-Hill Book Company, Inc., New York. Price, $4.95.

Untersuchung und Beurteilung des Herzkranken. By Professor Dr. Dr. h.c.H.W. KNIPPING, Prof. Dr. W. BOLT, Doz. Dr. H. VALENTIN, und Doz. Dr. H. VENRATH. 638 pages. 1960. Published by Ferdinand Enke, Stuttgart.

Visual Aids in Cardiologic Diagnosis and Treatment. Sponsored by the American College of Chest Physicians. Edited by ARTHUR M. MASTER, M.D., and EPHRAIM DONOSO, M.D., with 23 contributors. 216 pages; 26 × 17.5 cm. 1960. Grune & Stratton, New York. Price, $10.00.